INTERNAL MEDICINE

□ CASE REPORT □

Cases with Refractory Ascites and a Delayed Response to Tolvaptan

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Abstract

The patient was a 67-year-old female with liver cirrhosis due to hepatitis C. She was administered furosemide at 20 mg/day and spironolactone at 25 mg/day, but the ascites did not improve. Despite the additional administration of tolvaptan at 3.75 mg/day, the response to ascites was still poor. While the dose of tolvaptan was thereafter increased to 7.5 mg/day on the 7th hospital day, the ascites still persisted. However, she continued to receive tolvaptan (7.5 mg/day) because the worsening of her subjective symptoms was mild and she wished to do so. The ascites was later found to have almost completely disappeared on computed tomography (CT) at 6 months.

Key words: tolvaptan, liver cirrhosis, refractory ascites, delayed response

(Intern Med 55: 3273-3277, 2016)
(DOI: 10.2169/internalmedicine.55.7035)

Introduction

Conventionally, aldosterone antagonists and loop diuretics have been used for the management of ascites associated with liver cirrhosis (1, 2). However, some patients show poor responses or adverse reactions, such as renal dysfunction and electrolyte abnormalities, especially with high-dose administration and combined use. Tolvaptan is a vasopressin receptor antagonist and it shows a diuretic effect without Na excretion. It was approved as a concomitant medication for fluid retention in liver cirrhosis patients that insufficiently respond to existing diuretics for the first time in the world in September 2013 (3). Reportedly, there are some non-responders to tolvaptan, while others exhibit a delayed response after sustained administration. We herein report a patient in whom tolvaptan began to show an effect at least 2 months after the start of its administration.

Case Report

The patient was a 67-year-old female. During outpatient treatment for hepatitis C at a local clinic, hepatpcellular carcinoma (HCC) was detected in the right lobe of the liver, and percutaneous radiofrequency ablation was performed at our hospital on November, 2012. The patient was thereafter followed up at our hospital as an outpatient, but she developed anorexia and abdominal fullness in April 2014. Despite the administration of furosemide at 20 mg/day and spironolactone at 25 mg/day, the ascites did not decrease. The patient was admitted for the treatment of ascites on May, 2014. She had a history of cerebral infarction, but no particular familial history. She also had no history of interferon therapy for hepatitis C. The blood chemical analyses at the time of admission are shown in Table 1. The Child-Pugh score was 10 with grade C. Hyponatremia and marked renal dysfunction were also noted. The platelet count was markedly reduced at 37,000 cells/mL. Both alpha-fetoprotein (AFP) and des-gamma carboxyprothrombin (DCP) were mildly increased. Abdominal computed tomography (CT) before admission showed an irregularity of the liver surface, and the marked accumulation of ascites was observed. No signs of any recurrence of HCC were observed (Fig. 1a).

The course after admission is presented in Fig. 2. On admission, her body weight was 37.6 kg, and the daily urine volume was around 900 mL. While the administration of tolvaptan was initiated at 3.75 mg on the 1st hospital day, the urine volume did not increase with a slight increase in

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Received for publication December 23, 2015; Accepted for publication March 21, 2016
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Table 1. **Laboratory Data on Admission.**

Blood count		*Urinalysis*	
WBC	3,400μL	Urine osmolarity	N.E.
Hb	10.3g/dL	Decrease rate	N.E.
PLT	3.7×10^{4}/μL		
Coagulability		*Dose of diuretics*	
PT	65.6%	Furosemide	20mg/day
Biochemical values		Spironolactone	25mg/day
Na	130mEq/L	*Initail dose of tolvaptan*	3.75mg/day
K	3.9mEq/L		
BUN	72mg/dL	*Complication by HCC*	None(after cure)
Cr	2.19mg/dL		
eGFR	18	*TM*	
Alb	2.6g/dL	AFP	13ng/mL
T-bil	0.4mg/dL	DCP	50mAU/mL
ALT	28IU/L		
CRP	0.3mg/dL		

WBC: white blood cell, Hb: hemoglobin, PLT: platelet, PT: prothrombin time, Na: sodium, K: potassium, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, Alb: albumin, T-Bil: total bilirubin, ALT: alanine aminotransferase, N.E.: not evaluate, CRP: C-reactive protein, TM: tumor marker, HCC: hepatocellular carcinoma

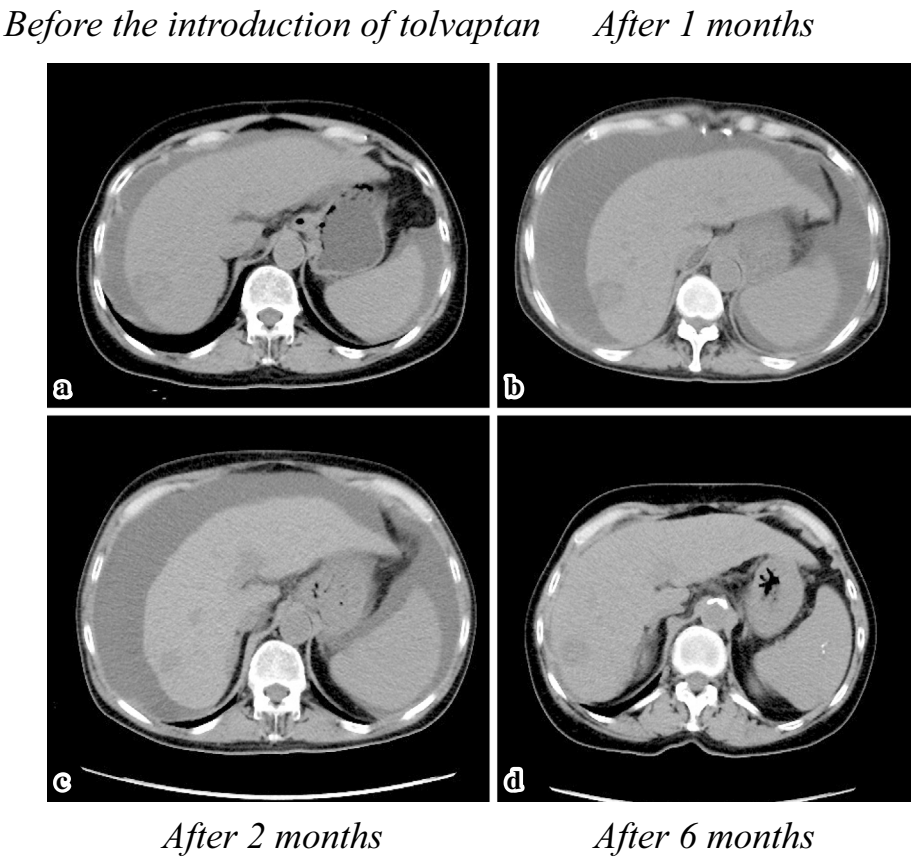

Figure 1. **(a) Abdominal CT performed 2 months before TLV administration showed cirrhosis with massive ascites. (b) A comparison of the abdominal CT performed 2 months before TLV administration with that performed 1 month after TLV administration revealed an increase in ascites. (c) A comparison of abdominal CT performed 1 month after TLV administration with that performed 2 months after TLV administration showed no significant increase or decrease in ascites. (d) Abdominal CT performed 6 months after TLV administration showed a significant decrease in ascites.**

her body weight; the dose of tolvaptan was thene increased to 7.5 mg on the 7th hospital day. Thereafter, although the urine volume showed no marked increase, the increase of her body weight became mild, and the patient was discharged on the 12th hospital day at her request. The water intake underwent a change of approximately 1,000 mL/day,

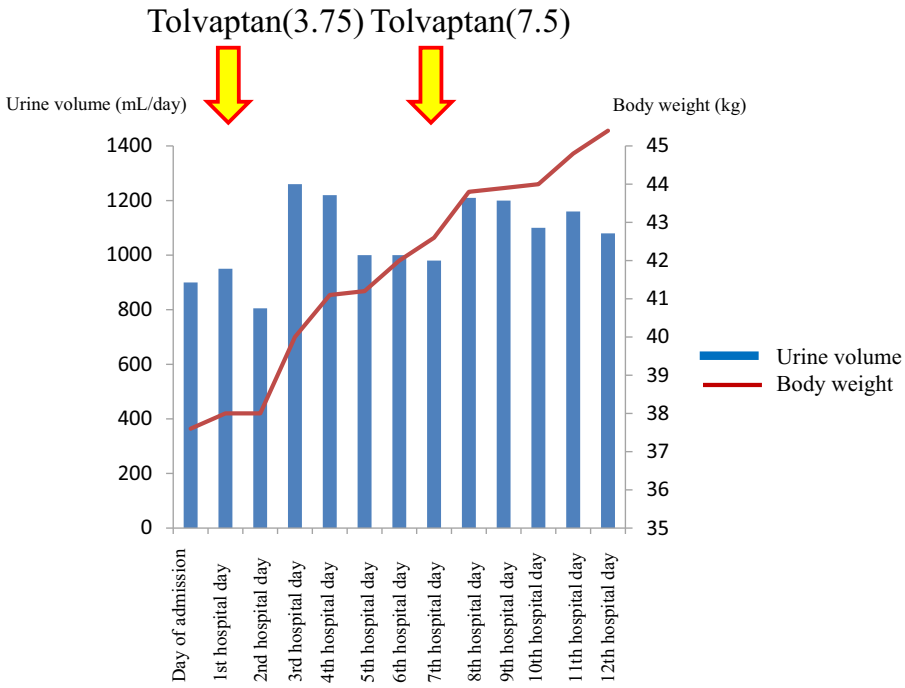

Figure 2. **Clinical course after admission; Despite the administration of tolvaptan at 3.75 mg on the 1st hospital day, no increase in urine volume or decrease in body weight was noted. Therefore, the dose of tolvaptan was increased to 7.5 mg on the 7th hospital day, but there was still no increase in urine volume or decrease in body weight.**

but the intake of fluids included with her meals clearly increased because the symptoms of anorexia also improved after admission. A comparison of the abdominal CT performed 2 months before tolvaptan administration with that performed 1 month after tolvaptan administration showed an increase in ascites (Fig. 1b), and the patient had clearly gained weight from 37.6 kg immediately before tolvaptan administration to 52.2 kg. However, she continued to receive only tolvaptan at 7.5 mg/day without any other additional treatment, such as cell-free and concentrated ascites reinfusion therapy (CART) because the worsening of her subjective symptoms was mild and she wished to do so. A comparison of the CT performed 1 month after tolvaptan administration with that performed 2 months after tolvaptan administration revealed no significant increase or decrease in ascites (Fig. 1c). However, she showed a weight loss from 52.2 to 49.9 kg; therefore, she continued to receive tolvaptan at 7.5 mg/day. After tolvaptan administration, no additional treatment for ascites was given. The abdominal CT performed at 6 months revealed the ascites to have markedly decreased (Fig. 1d). Therefore, the oral administration of furosemide was discontinued, and the administration of only spironolactone at 25 mg and tolvaptan at 7.5 mg was continued. After the beginning of tolvaptan administration, no adverse reaction such as liver and kidney dysfunction was observed.

Discussion

In cirrhotic patients, splanchnic vasodilation, an increase of portal vein pressure and portosystemic shunt result in a decreased effective arterial blood volume. A consequent decrease in the renal blood flow is considered to induce fluid retention through the activation of the renin-angiotensin-aldosterone system (4, 5). Although, aldosterone receptor antagonists are effective for the treatment of fluid retention associated with liver cirrhosis (1), it is insufficient in many patients. Fluid retention is also caused by the activation of vasopressin (VP) through the decrease in the circulating plasma volume (4, 5), but there is still no available medication that has been shown to be effective for the activation of VP.

Tolvaptan is an antagonist for vasopressin V2 receptors in the collecting ducts of the kidney, and it exerts a diuretic effect by suppressing the expression of aquaporin 2. In Japan, a phase 3 comparative study of tolvaptan was carried out in cirrhosis patients who responded poorly to the administration of loop diuretics and anti-aldosterone agents (3). According to the phase 3 study, the urine volume significantly increased on Days 1 and 7 in the tolvaptan group, but no significant change was observed in the placebo group. Thirst, constipation, kidney dysfunction, hepatic encephalopathy, and itching were noted as major adverse reactions, but their severity was only mild to moderate.

Various studies have been reported regarding the prediction of the effect of tolvaptan. Zhang et al. investigated 39 liver cirrhosis patients accompanied by refractory ascites, and observed the effect of tolvaptan to be attenuated in the patients with hepatorenal syndrome (HRS) (6). The effect of tolvaptan has also been reported to decrease as the estimated

Table 2. Time-course of Laboratory Data.

	On admission	After 14 days	After 1 month	After 2 months	After 6 months
Blood count					
WBC	3,400μL	3,900μL	5,200μL	4,000μL	2,700μL
Hb	10.3g/dL	9.8g/dL	10.9g/dL	8.3g/dL	9.9g/dL
PLT	3.7×10^{4}/μL	6.2×10^{4}/μL	10.8×10^{4}/μL	7.6×10^{4}/μL	10.9×10^{4}/μL
Coagulability					
PT	65.6%	75.8%	77.7%	62.6%	70.9%
Biochemical values					
Na	130mEq/L	140mEq/L	143mEq/L	144mEq/L	141mEq/L
K	3.9mEq/L	4.9mEq/L	5.0mEq/L	4.9mEq/L	4.7mEq/L
BUN	72mg/dL	27mg/dL	30mg/dL	23mg/dL	29mg/dL
Cr	2.19mg/dL	1.34mg/dL	1.45mg/dL	1.22mg/dL	1.20mg/dL
eGFR	18	31	29	35	35
Alb	2.6g/dL	2.4g/dL	2.9g/dL	2.6g/dL	2.8g/dL
T-bil	0.4mg/dL	0.4mg/dL	0.7mg/dL	0.5mg/dL	0.7mg/dL
ALT	28IU/L	27IU/L	27IU/L	20IU/L	34IU/L
CRP	0.33mg/dL	0.23mg/dL	0.25mg/dL	0.55mg/dL	0.04mg/dL

WBC: white blood cell, Hb: hemoglobin, PLT: platelet, PT: prothrombin time, Na: sodium, K: potassium, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, Alb: albumin, T-Bil: total bilirubin, ALT: alanine aminotransferase, CRP: C-reactive protein

glemerular filtration rate (eGFR) decreased in renal failure patients in a single-dose study of tolvaptan (7). In a phase 3 clinical study in Japan, the effect of tolvaptan decreased when blood urea nitrogen (BUN) was high in a subanalysis (8). In addition, the effect of tolvaptan decreased in patients demonstrating renal parenchymal disorder with HRS and a decreased eGFR and those with high BUN, i.e., patients suggested to have intravascular volume depletion and prerenal renal dysfunction. The present patient had severe anorexia and prerenal renal dysfunction with 72 mg/dL BUN and 2.19 mg/dL creatinine (Cr) before admission, and these conditions may have been the cause of the poor effect of tolvaptan early after the initiation of administration. However, the symptoms of anorexia improved after admission, where the renal function markedly improved and BUN and Cr on day 14 after the initiation of tolvaptan administration were 27 and 1.34 mg/dL, respectively (Table 2). On the other hand, no reduction in the body weight or ascites was observed for at least 2 months after the initiation of tolvaptan administration. Thus, it is difficult to explain the cause of the poor effect of tolvaptan early after the initiation of administration with renal dysfunction alone. However, although both the ascites and the body weight (37.6→52.2 kg) clearly increased one month after the introduction of tolvaptan compared with those before introduction, no change in body weight was observed over the next month (52.2→49.9 kg). Therefore, it is conceivable that the renal dysfunction caused by dehydration could have blocked the effect of tolvaptan in the early course of tolvaptan treatment. Thereafter the effect of tolvaptan gradually increased after the initial course.

We herein presented a case showing a delayed effect of tolvaptan. Therefore, even when the initial responses of the urine volume and body weight are not remarkable, the continuation of tolvaptan administration should be considered if there is no exacerbation of ascites. Although the safety of long-term tolvaptan therapy has been reported (9), further studies involving more patients are needed before any definitive conclusions can be made.

The authors state that they have no Conflict of Interest (COI).

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