

Case Report

Tolvaptan for Primary Aldosteronism and Autosomal Dominant Polycystic Kidney Disease: A Case Report

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Keywords

Tolvaptan · Autosomal dominant polycystic kidney disease · Primary aldosteronism

Abstract

A 59-year-old Japanese woman was admitted for evaluation of muscle weakness. Autosomal dominant polycystic kidney disease had been diagnosed at the age of 47 years, followed by primary aldosteronism at 53 years. At the age of 58, tolvaptan was started (60 mg/day) to treat her renal disease. After 8 months of tolvaptan therapy, hypokalemia-related muscle weakness became prominent, and hypertension became refractory. Finally, treatment with low-dose tolvaptan (30 mg/day) and high-dose spironolactone (100 mg/day) normalized

serum potassium and the blood pressure. Tolvaptan can induce urinary excretion of potassium in patients with primary aldosteronism, and possible mechanisms are discussed.

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Introduction

Torres et al. [1] reported that tolvaptan (a vasopressin V2 receptor antagonist) slowed the increase of the total kidney volume and decline of renal function over a 3-year period in patients with autosomal dominant polycystic kidney disease (ADPKD) compared to placebo. In addition, Muto et al. [2] reported that tolvaptan was effective in 118 Japanese patients with ADPKD, since it reduced the annual growth rate of total kidney volume and slowed the decline of kidney function over 36 months. Tolvaptan was approved as an option for the medical treatment of ADPKD patients in Japan. In the above 2 studies, hypokalemia was not noted as a serious complication. We treated a 59-year-old Japanese woman with ADPKD and primary aldosteronism. Eight months after starting tolvaptan therapy, she developed definite hypokalemia-related muscle weakness, and her hypertension became refractory. The influence of tolvaptan on potassium metabolism in this patient is discussed.

Case Report

A 59-year-old Japanese woman was admitted to our hospital for evaluation of muscle weakness. Hypertension had been detected at the age of 30 years. When she was 47, ADPKD was diagnosed because computed tomography showed polycystic kidneys and her father had this disease. At 53 years, primary aldosteronism was diagnosed after detection of hypokalemia and a left adrenal tumor. Spironolactone was administered. An angiotensin II receptor blocker (ARB; olmesartan at 40 mg/day) was added to treat hypertension, after which her blood pressure and serum potassium level were normalized despite discontinuation of spironolactone (Table 1). At 58 years, tolvaptan therapy was started at 60 mg/day (morning and afternoon doses of 45 and 15 mg) to treat her renal disease (Table 1; Fig. 1). Hypertension became more severe after the initiation of tolvaptan. Although the dual action beta blocker/alpha-1 blocker carvedilol (15 mg/day), calcium channel blocker cilnidipine (20 mg/day), and ARB telmisartan (40 mg/day) were added, her hypertension was not controlled. Eight months after starting tolvaptan, muscle weakness and numbness of the lower limbs became problematic. At 12 months, she was admitted to our hospital.

On admission, the patient was 152 cm tall, weighed 61 kg, and had a blood pressure of 182/84 mm Hg. Laboratory tests revealed that serum creatinine was 1.1 mg/dL (eGFR: 39.7 mL/min/1.73 m²), urea nitrogen was 24 mg/dL, Na was 144 mmol/L, K was 2.5 mmol/L, and Cl was 99 mmol/L. Renin activity was <0.2 ng/mL/h (normal: 0.3–2.3), and the aldosterone concentration was 130 ng/dL (normal: 3.0–15.0). Urinary K excretion was 65 mmol/day, Na excretion was 130 mmol/day, and Cl excretion was 120 mmol/day (Table 1).

Clinical Course

Before admission, hypokalemia was exacerbated after starting tolvaptan therapy, and her hypertension became refractory (Fig. 2). The patient hoped to continue tolvaptan use. Therefore, a potassium supplement was administered, but her serum potassium only increased to 3.5 mmol/L. Tolvaptan was discontinued temporarily, and serum potassium increased to 4.0 mmol/L. Next, tolvaptan (60 mg/day) and spironolactone (50 mg/day) were administered concomitantly, but the serum potassium level dropped to 3.0 mmol/L. Subsequently, tolvaptan was tapered to a daily dose of 30 mg, and spironolactone was increased to a daily dose of 100 mg. Thereafter, serum potassium remained above 4.0 mmol/L, and control of the blood pressure improved.

Discussion

In this patient, hypokalemia and hypertension related to primary aldosteronism were initially controlled by spironolactone and then by an ARB alone, even after spironolactone had been discontinued. Hypokalemia became more pronounced after the patient started tolvaptan therapy, probably due to excessive excretion of potassium, and could not be corrected by administration of a potassium supplement. Discontinuation of tolvaptan led to normalization of serum potassium and better control of hypertension. Finally, treatment with low-dose tolvaptan (30 mg/day) and high-dose spironolactone (100 mg/day) achieved normalization of serum potassium as well as blood pressure. The mechanism of hypokalemia in this patient after administration of tolvaptan is interesting.

Torres et al. [1] investigated the effects of tolvaptan in 961 patients participating in the ADPKD TEMPO 3:4 clinical trials. Hypokalemia was not reported as an adverse effect, although hyponatremia was considered to require attention. Kim et al. [3] reported on the pharmacokinetics, pharmacodynamics, and safety of tolvaptan in healthy Japanese subjects. They stated that the serum sodium concentration was increased by tolvaptan and was higher than with placebo, even 24 h after dosing, while serum potassium was unchanged. These studies indicate that tolvaptan does not affect potassium metabolism, even though urinary water and sodium excretion is affected by higher doses of tolvaptan.

In our patient, serum and urinary K levels at the time of admission were 2.5 mmol/L and 65 mmol/day, respectively, indicating the urinary K loss as a cause of hypokalemia. Although tolvaptan alone did not alter urinary K excretion (as stated above) it may have affected aldosterone secretion and/or aldosterone signaling in the kidney. Concomitant progression of hypokalemia and hypertension after tolvaptan treatment in the presented case supports the possibility [4]. Moreover, discontinuation of tolvaptan ameliorated hypokalemia (Fig. 2). As for the role of vasopressin in the adrenal gland, previous studies have shown that vasopressin V1a receptor is present in the adrenal cortex, where it regulates adrenal hormone secretion. More interestingly, vasopressin (but not desmopressin) increased aldosterone secretion in a patient with aldosterone-producing adenoma, which is likely due to aberrant receptor signaling in the adenoma [5]. Given the evidence, it may be that a high-dose tolvaptan treatment elevated plasma ADH levels, which may have promoted aldosterone secretion in the tumor through V1 receptor signaling. Unfortunately, however, the temporal profile of plasma renin and aldosterone levels is not available. In addition to this mechanism, inhibi-

tion of Na-Cl cotransporter (NCC) activity may have contributed to the occurrence of severe hypokalemia. Insights from recent studies suggest that NCC activation counteracts the progressive decrease in plasma K levels in primary aldosteronism [6]. Because several studies have suggested that the angiotensin II and also vasopressin V2 receptor pathways increase NCC activity independently of aldosterone [7, 8], the administration of high-dose ARB and tolvaptan may have acted to reduce NCC, which permitted the urinary K loss and occurrence of severe hypokalemia by increasing distal Na delivery. Polyuria and increased activity of flow-induced K secretion might also need to be considered. Although mechanisms are not entirely clear, the present case clearly illustrates that V2 receptor antagonism can modulate aldosterone signaling and worsen the clinical course of primary aldosteronism.

In conclusion, tolvaptan does not normally influence potassium regulation. However, in patients with primary aldosteronism, tolvaptan can induce urinary excretion of potassium. Although the mechanisms need further investigation, aberrant V1 receptor signaling in the adrenal gland and also the modulation of NCC activity in the kidney may play a role, leading to hypokalemia and refractory hypertension. In our patient with primary aldosterone and ADPKD, addition of spironolactone allowed continuation of tolvaptan therapy by stimulating NCC activity.

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Statement of Ethics

Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with human participants performed by any of the authors.

Disclosures Statement

The authors declare that they have no conflicts of interest to disclose.

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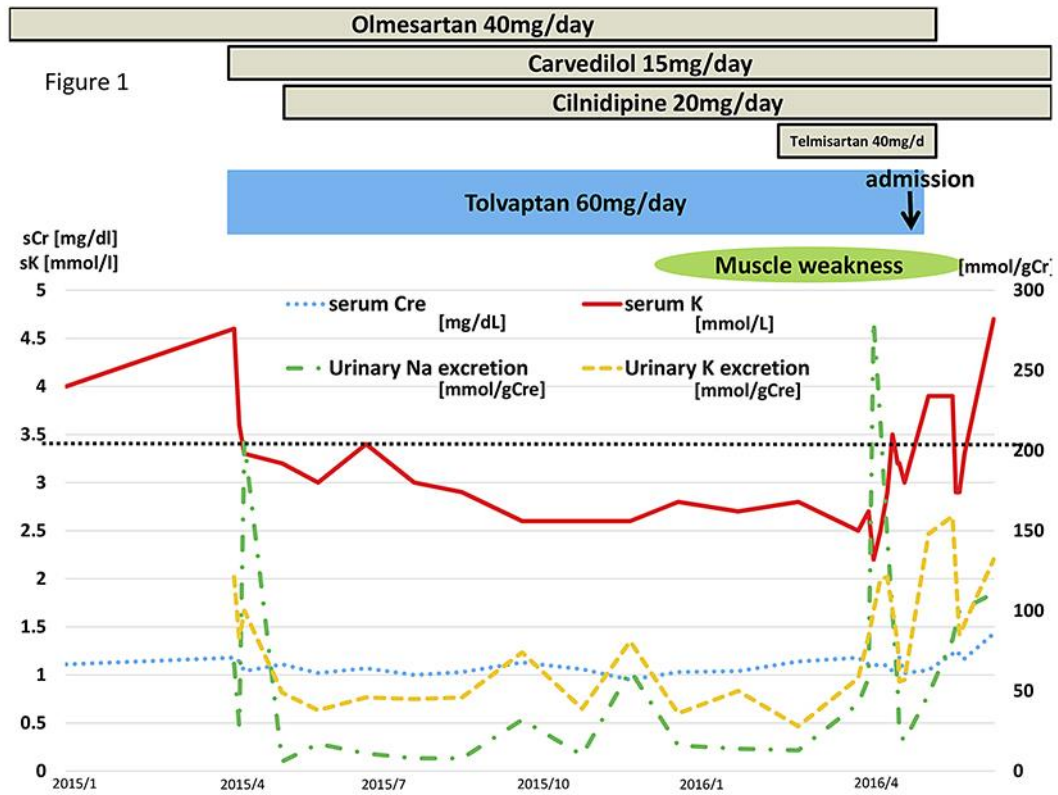


Fig. 1. Clinical course part 1: the clinical course before admission.

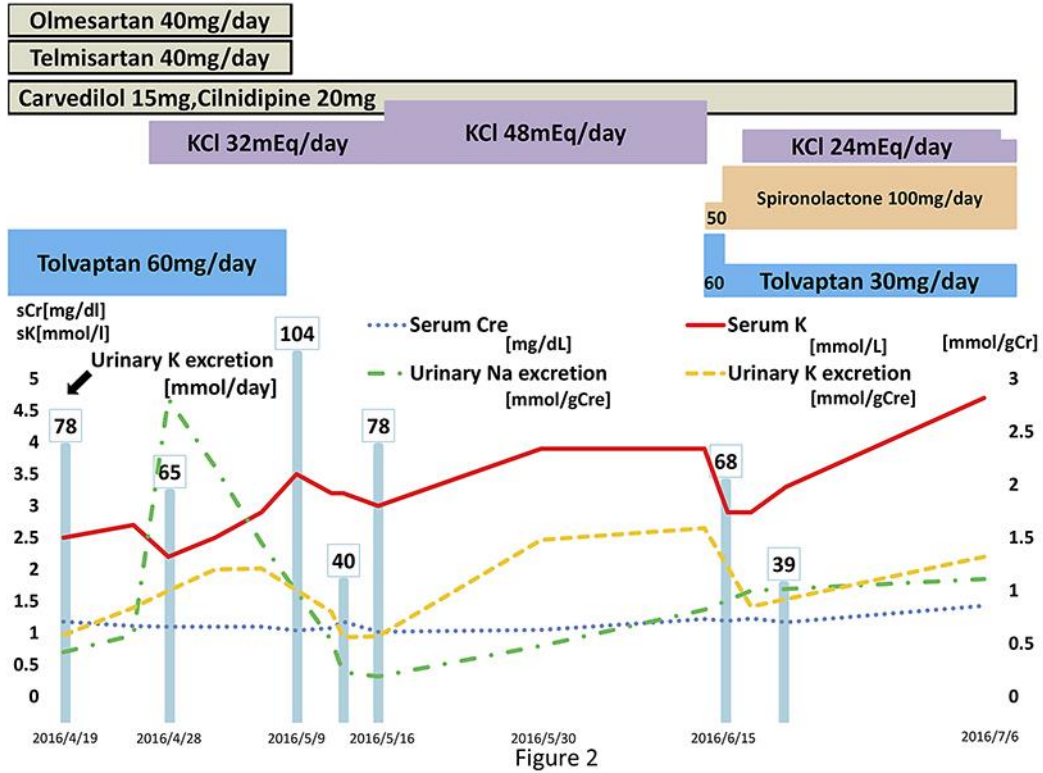


Fig. 2. Clinical course part 2: the clinical course after admission.

Table 1. Patient data before therapy and after 12 months

	Before	After 12 months	Normal range		Before	After 12 months	Normal range
White blood cell, / μ L	4,700	6,700	3,400–9,200	CRP, mg/dL	7.1	0.1	0.0–0.3
Red blood cell, $\times 10^6$ / μ L	406	402	400–566				
Hemoglobin, g/dL	13.5	12.7	13.0–17.0	Urinalysis			
Hematocrit, %	39.4	36.8	38.2–50.8	Glucose	Negative	Negative	Negative
Platelet, $\times 10^3$ / μ L	13.7	16	14.1–32.7	Sediment			
Total protein, g/dL	7.1	7.3	6.9–8.4	RBC, /HPF	>100	1–4	<1
Albumin, g/dl	3.9	3.8	3.9–5.2	WBC, /HPF	1–4	<1	<1
Total bilirubin, mg/dL	0.5	0.6	0.3–1.1	Cast	None	None	<1
AST, IU/L	20	24	13–33	Protein, g/day	0.3	2.6	
ALT, IU/L	14	16	8–42	NAG, IU/day	4.3	15.1	0.8–5.0
LDH, IU/L	221	302	119–229	α 1 MG, mg/day	3.8	12.9	0.6–8.8
CPK, IU/L	95	193	62–287	β 2 MG, μ g/day	1	11.1	0.1–1.9
ALP, IU/L	185	214	117–350	Na, mmol/day	37	130	40–400
γ GTP, IU/L	39	37	9–109	K, mmol/day	33	65	10–120
UN, mg/dL	28	24	8–12	Cl, mmol/d	73	120	50–400
Creatinine, mg/dL	1.2	1.2	0.65–1.06	Ca, mg/day	50	38	40–200
eGFR, ml/min/1.73 m ³	37.3	37.1	>100	P, g/day	0.94	0.72	0.2–1.0
Urinary acid, mg/dL	8.2	9.2	2.5–7.0	Cre, g/day	2.3	2.5	0.7–2.5
Na, mmol/L	141	144	139–146	Renin, ng/mL/h	<0.2	0.2	0.3–2.3
K, mmol/L	4.6	2.5	3.7–4.8	Aldosterone, ng/dL	131	138	3.0–15.0
Cl, mmol/L	105	99	101–108				
Ca, mmol/L	9.9	9.2	8.7–10.1				
P, mmol/L	4.4	4.3	2.8–4.6				
CRP, mg/dL	0.3	0.4	0.0–0.3				