JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
LETTER TO THE EDITOR

Pseudoaldosteronism induced by Yokukansan in an elderly Japanese type 2 diabetic patient with Alzheimer's disease

The number of patients with Alzheimer's disease (AD), and/or behavioral and psychological symptoms of dementia (BPSD) has been markedly increasing all over the world, and has become a social and health problem. Furthermore, it has been recently established that the diabetic condition is a major risk factor for the development of dementia[1]. Second-generation antipsychotics have been used, but some cases are refractory[2]. Yokukansan is a licorice-containing Chinese medicine, and has been very often used for the treatment of such disease[3]. A previous report showed that Yokukansan exerts beneficial effects and can be used very safely[3]. It is known that a large amount of licorice could induce pseudoaldosteronism, but Yokukansan contains only a small amount of licorice. Therefore, it has been thought that the use of Yokukansan does not lead to the onset of pseudoaldosteronism. However, here we report a case of pseudaldosteronism that developed after starting Yokukansan in an elderly Japanese diabetic patient with AD and BPSD.

In February 2013, a 77-year-old Japanese man with type 2 diabetes was admitted to the Kawasaki Medical School, Kurashiki, Japan, because of hypokalemia and weight gain. He had been taking Yokukansan for 5 months (7.5 g/day containing 1.5 g of licorice). He frequently felt general fatigue, and his bodyweight was increased by 7 kg. On admission, his bodyweight was 64.3 kg and height 160.5 cm. He did not have vomiting or diarrhea and did not use any diuretics. Physical examination revealed mild systolic hypertension. Marked pretibial pitting edema was observed in the bilateral lower extremities. Table 1 shows the laboratory findings on admission. Serum potassium was 3.0 mEq/L with mild renal dysfunction. The low-renin and low-aldosterone state was observed with concomitant metabolic alkalosis. In addition, the transtubular potassium gra-

Table 1 | Laboratory findings on admission

CBC		*Endocrinology*	
WBC	7600/μL	PRA	0.2 ng/mL/h
Hb	11.6 g/dL	PAC	<10.0 pg/mL
Plt	11.7 × 10^4/μL	ACTH	56.7 pg/mL
Blood chemistry		Cortisol	11.4 μg/dL
Alb	2.9 g/dL	DHEA-S	52 μg/dL
T-bil	0.4 mg/dL	BNP	129.2 pg/mL
ALP	226 IU/L	TSH	4.35 μIU/mL
AST	32 IU/L	FT3	2.90 pg/mL
ALT	18 IU/L	FT4	1.06 ng/dL
LDH	404 IU/L	*Diabetes*	
BUN	12 mg/dL	FPG	119 mg/dL
Cre	1.29 mg/dL	HbA1c	7.7%
UA	4.6 mg/dL	GA	19.0%
CRP	0.04 mg/dL	IRI	2.2 μIU/mL
Electrolyte		*Lipid*	
Na	143 mEq/L	TC	231 mg/dL
K	3.0 mEq/L	LDL-C	132 mg/dL
Cl	104 mEq/L	HDL-C	52 mg/dL
Ca	8.2 mg/dL	TG	125 mg/dL
IP	3.1 mg/dL	*Urinalysis*	
Mg	2.1 mg/dL	pH	6.5
Osmolality	298 mOsm/kg	S.G.	1.019
Blood gas analysis		protein	3+
pH	7.456	Occult blood	2+
pCO_2	45.8 mmHg	Ketone body	Negative
pO_2	64.0 mmHg	Na	51 mEq/L
HCO^3–	31.6 mEq/L	K	44 mEq/L
BE	6.6 mEq/L	Cl	39 mEq/L
Lactate	0.70 mEq/L	Osmolality	279 mOsm/kg

ACTH, adrenocorticotropic hormone; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BE, base excess; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cre, creatinine; CRP, C-reactive protein; DHEA-S, dehydroepiandrosterone sulfate; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; GA, glycoalbumin; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IRI, imunoreactive insulin; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; PAC, plasma aldosterone concentration; Plt, platelet; PRA, plasma renin activity; S.G., specific gravity; T-bil, total bilirubin; TC, total cholesterol; TG, triglyceride; TSH, thyroid-stimulating hormone; UA, uric acid; WBC, white blood cells.

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Received 12 September 2014; revised 30 September 2014; accepted 5 October 2014

dient (TTKG) was very high (11.0). Given these findings, we made the diagnosis of Yokukansan-induced pseudoaldsteronism, and stopped this drug. After commencement of oral potassium replacement, potassium level was increased (3.8 mEq/L at day 10) and TTKG was decreased to 3.5. Pitting edema disappeared with 6-kg weight reduction. On day 20, he was discharged from the hospital.

Recently, Yokukansan has been very often used for dementia, and its sales amount has been drastically increasing. It has been thought that Yokukansan can be used very safely[3]. To the best of our knowledge, this is the first report showing that Yokukansan induced pseudoaldosteronism in diabetic patients. The mechanism of how licorice causes pseudoaldosteronism is likely through the inhibition of renal enzyme 11-hydroxysteroid dehydrogenase type 2. Cortisol, as well as aldosterone, can bind to the mineralocorticoid receptor (MR), but, 11-hydroxysteroid dehydrogenase type 2 converts cortisol to cortisone that does not work on MR. As a result, aldosterone dominantly binds to MR[4]. However, licorice inactivates 11-hydroxysteroid dehydrogenase type 2 and increases the cortisol binding to MR, which explains the mechanism for licorice-induced pseudoaldosteronism.

It is known that the onset of pseudoaldosteronism depends on the dose of licorice, but the present case developed pseudoaldosteronism with a very low dose of licorice (1.5 g/day).

In fact, a similar frail and elderly female case of Yokukansan-induced pseudoaldosteronism with severe hypokalemia was reported by Nishiya *et al.*[5] Thereby, we should pay careful attention when using Yokukansan, even with a low-dose component of licorice. Taken together, we should consider the possibility of pseudoaldosteronism when we use Yokukansan for dementia, and careful monitoring of electrolytes, especially potassium, is necessary.

ACKNOWLEDGMENT

The authors declare no conflict of interest.

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Doi: 10.1111/jdi.12297