Severe metabolic alkalosis, hypokalemia, and respiratory acidosis induced by the Chinese herbal medicine yokukansan in an elderly patient with muscle weakness and drowsiness

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Abstract Yokukansan is a Chinese herbal medicine containing licorice that has been shown to alleviate the behavioral and psychological symptoms of Alzheimer's disease, with few adverse effects. Increasing numbers of patients with Alzheimer's disease in Japan are now being treated with this drug. However, yokukansan should be used with caution because of its potential to induce pseudoaldosteronism through the inhibition of 11-beta-hydroxysteroid dehydrogenase type 2, which metabolizes cortisol into cortisone. We present the case of an 88-year-old woman with a history of Alzheimer's disease who was transferred to our emergency department because of drowsiness, anorexia, and muscle weakness. Her blood pressure was 168/90 mmHg. Laboratory data showed serum potassium of 1.9 mmol/l, metabolic alkalosis (pH 7.54; HCO_3^- , 50.5 mmol/l; chloride, 81 mmol/l; sodium, 140 mmol/l), and respiratory disorders (pCO_2 , 60.5 mmHg; pO_2 , 63.8 mmHg). Plasma renin activity and aldosterone concentration were suppressed, and urinary potassium excretion was 22 mmol/l (calculated transtubular potassium gradient 12.9). An electrocardiogram showed flat T-waves and U-waves with ventricular premature contractions.

Echocardiography denied volume depletion. Medical interview disclosed that she had been treated with a Chinese herbal medicine (yokukansan) containing licorice. The final diagnosis was pseudoaldosteronism and respiratory acidosis induced by licorice. Hypokalemia, metabolic alkalosis, and respiratory acidosis all subsided shortly after the discontinuation of yokukansan and initiation of intravenous potassium replacement. This case highlights the need for nephrologists to consider the possible involvement of Chinese herbal medicines, including yokukansan, when they encounter hypokalemia in elderly patients.

Keywords Herbal medicine · Hypokalemia · Metabolic alkalosis · Licorice · Yokukansan

Introduction

Hypokalemia is an important electrolyte disorder occasionally seen in elderly patients [1]. The serum potassium (K) level is determined mainly by the balance among oral intake, distribution, and excretion via the kidney and the gastrointestinal tract [2]. Although hypokalemia in elderly patients is often attributed to decreased K intake or K loss through the gastrointestinal tract, it can be caused by urinary K loss as a side effect of drug administration [3–6].

Several investigators have recently shown that the Chinese herbal medicine yokukansan can alleviate the behavioral and psychological symptoms of dementia (BPSD), such as hallucinations, delusions, agitation, aggression, and wandering, in patients with Alzheimer's disease, with few side effects [7–9]. The numbers of elderly people with Alzheimer's disease have been increasing, and drugs that can safely and effectively mitigate BPSD are, therefore, in demand. However, some herbal medicines, including

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yokukansan, contain licorice and can occasionally cause pseudoaldosteronism by inhibiting endogenous 11-beta-hydroxysteroid dehydrogenase type 2 (11 β -HSD2), resulting in mild to severe hypokalemia and metabolic alkalosis [5, 6].

We describe here the case of an elderly patient treated with yokukansan, who developed severe hypokalemia, metabolic alkalosis, and respiratory acidosis related to muscle weakness.

Case report

An 88-year-old woman was transferred to our hospital because of drowsiness, muscle weakness, and anorexia. She had been receiving care at a nursing home for the last 3 years because of worsening Alzheimer's disease. Her medical history included replacement of bilateral femoral heads at ages 81 and 83 years, respectively. Six months before admission, yokukansan treatment was initiated to control BPSD related to Alzheimer's disease. However,

3 weeks after the start of yokukansan treatment, she developed constipation, and a laxative was administered. Her serum K and chloride (Cl) levels just prior to starting yokukansan treatment were 4.2 and 101 mmol/l, respectively.

On admission, she was somnolent. Her height was 154 cm and body weight was 38.4 kg. Her blood pressure was 168/90 mmHg, heart rate 88 beats per minute, body temperature 37.8 °C, and respiratory rate 10/min. Physical examination revealed that both patellar and plantar reflex were attenuated, and her respiration was shallow. Muscle strength in her limbs was also weakened. Pretibial pitting edema was observed bilaterally. Her biochemical parameters and urinary findings are summarized in Table 1. Serum sodium (Na) was 140 mmol/l; K, 1.9 mmol/l; Cl, 81 mmol/l; and C-reactive protein, 6.0 mg/dl. Urinary levels of Na, K, and Cl were 45, 22, and 43 mmol/l, respectively. Urinalysis revealed bacteriuria and leukocyturia, indicating concomitant urinary tract infection. Arterial blood gas analysis revealed pH 7.54; pO₂, 63.8 mmHg (O₂ 0.5 l/min, nasal cannula); pCO₂, 60.5 mmHg; and HCO₃⁻, 50.5 mmol/l. Plasma renin activity and aldosterone

Table 1 Laboratory data on admission

Complete blood count		Urinalysis and urinary sediment	
White blood cell count, / μ l	6900	pH (dipstick)	7.0
Hemoglobin, g/dl	12.2	Specific gravity (dipstick)	1.010
Platelets, $\times 10^4$ / μ l	22.7	Protein (dipstick)	$\pm$
Biochemistry		Hematuria (dipstick)	Negative
Total protein, g/dl	5.4	Bilirubin	Negative
Albumin, g/dL	3.0	Ketone	Negative
Total bilirubin, mg/dl	1.6	Bacteria	3 $\pm$
Aspartate aminotransferase, U/l	23	Red blood cell, high-power field	1–4
Alanine aminotransferase, U/l	14	White blood cell, high-power field	30–49
Lactate dehydrogenase, U/l	205	Epithelial cell, high-power field	10–19
Creatine phosphokinase, U/l	12	Urinary biochemistry	
Blood urea nitrogen, mg/dl	10.5	Sodium, mmol/l	45
Creatinine, mg/dl	0.62	Potassium, mmol/l	22
Uric acid, mg/dl	3.5	Chloride, mmol/l	43
Sodium, mmol/l	140	Urine osmolarity, mOsmol/kgH ₂ O	263
Potassium, mmol/l	1.9	Endocrinology	
Chloride, mmol/l	81	PRA, ng/ml/h	0.3
Magnesium, mg/dl	2.6	PAC, pg/ml	17.8
Calcium, mg/dl	8.6	TSH (serum), μ U/ml	1.33
Phosphorus, mg/dl	4.0	Free T4 (serum), ng/dl	1.23
Triglyceride, mg/dl	69	ACTH (plasma), pg/ml	59
Total cholesterol, mg/dl	194	Cortisol (serum), μ g/ml	18.4
LDL-cholesterol, mg/dl	109	Cortisol (urine), μ g/day	122
HDL-cholesterol, mg/dl	54	Blood gas analysis	
C-reactive protein, mg/dl	6.3	pH	7.54
Glucose, mg/dl	92	pO ₂ (O ₂ 0.5 l/min, nasal cannula), mmHg	63.8
HbA1c, %	4.5	pCO ₂ , mmHg	60.5
Plasma osmolarity, mOsmol/kgH ₂ O	275	HCO ₃ ⁻ , mmol/l	50.5

Serum was collected after fasting in the morning:

ACTH adrenocorticotrophic hormone, HDL high-density lipoprotein, LDL low-density lipoprotein, PAC plasma aldosterone concentration, PRA plasma renin activity, TSH thyroid-stimulating hormone

Fig. 1 Computed tomography of **a** the chest and **b** the abdomen on admission

Fig. 2 Clinical course during hospitalization. HCO_3^- bicarbonate, iv intravenous, K potassium, SBP systolic blood pressure, DBP diastolic blood pressure

concentration were 0.3 ng/ml/h (normal range; 0.3–2.9) and 17.8 pg/ml (normal range; 35.7–240), respectively. The calculated transtubular K gradient was 12.9. Endocrinological study revealed thyroid-stimulating hormone of 1.33 $\mu\text{g/ml}$, thyroxine of 1.23 $\mu\text{g/ml}$, adrenocorticotrophic hormone of 59 pg/ml, and cortisol of 18.4 $\mu\text{g/ml}$. Urinary cortisol was 122 $\mu\text{g/day}$ (normal range; 26–187). Echocardiography revealed preserved left ventricular systolic function and an inferior vena cava diameter of 15 mm. An electrocardiogram showed flat T-waves and U-waves in leads V2–V5 and ventricular premature contractions. The corrected QT interval was 485 ms. Computed tomography showed neither infiltrative lesions nor lung diseases, including chronic obstructive pulmonary disease (Fig. 1a). There was no mass in the adrenal glands and no signs of calcium deposition or calcinosis in the kidney (Fig. 1b). Her medications were oxidized magnesium 1.5 g/day, alfacalcidol 0.5 $\mu\text{g/day}$, and brotizolam 0.25 mg/day. However, she had also been treated with yokukansan 7.5 g/day, containing 4.5 g of licorice, and was, therefore,

finally diagnosed with licorice-induced pseudoaldosteronism, as a result of the inhibition of $11\beta\text{-HSD2}$ by the licorice.

Figure 2 summarizes the patient's clinical course during hospitalization. The administration of yokukansan was discontinued and intravenous K replacement was initiated from the first hospital day. The supplemental K dose was adjusted according to her daily serum and urinary K levels, ranging from 30 to 80 mmol/day, until the 11th hospital day. She was also treated with antibiotics for a coincident urinary tract infection, which subsided after 7 days of treatment. Ten days after starting K replacement therapy, serum K and Cl levels were normalized, and respiratory disorders improved (PaO_2 , 82 mmHg; PaCO_2 , 44 mmHg, under room air). Her transtubular K gradient was 4.2 at day 13 (serum K, 4.7 mmol/l; urinary K, 46 mmol/l; plasma osmolality, 292 mOsmol/kgH₂O; urinary osmolality, 670 mOsmol/kgH₂O). She was finally transferred back to the nursing home on the 14th hospital day under oral K supplementation. At discharge, the U-waves had disappeared and the

corrected QT interval was normalized on electrocardiogram. K supplementation was stopped 2 months after discharge and serum K remained normal at 3 months after discharge (plasma renin activity, 0.6 ng/ml/h; plasma aldosterone concentration, 34.9 pg/ml).

Discussion

There are a variety of differential diagnoses for hypokalemia with metabolic alkalosis [10]. These disorders are usually induced by increased mineralocorticoid activity, such as in Cushing syndrome, deoxycorticosterone-producing tumors, apparent mineralocorticoid excess syndrome, Bartter syndrome, Gitelman syndrome, Gordon syndrome, Conn syndrome, reninoma, and renal artery stenosis. In the present case, the patient showed hypokalemia, metabolic alkalosis, high urinary K excretion with high transtubular K gradient, hypertension with peripheral edema, suppressed renin–angiotensin–aldosterone axis, and a history of yokukansan use. Her adrenal and thyroid functions were normal. These findings were consistent with pseudoaldosteronism, and the patient was successfully treated by the discontinuation of yokukansan and intravenous K replacement.

Pseudoaldosteronism as a licorice-induced complication is an important pathogenesis of hypokalemia and metabolic alkalosis. Pseudoaldosteronism usually presents as hypertension (sodium retention), high urinary K and Cl excretion, hypokalemia, metabolic alkalosis (hypochloremia), and suppression of the renin–angiotensin–aldosterone system. Pseudoaldosteronism related to licorice is caused by its inhibition of 11 β -HSD2 activity, which converts active cortisol into inactive cortisone [11]. After licorice is metabolized into glycyrrhizin, glycyrrhizin blocks endogenous 11 β -HSD2, leading to the increase in cortisol, which can equally stimulate mineralocorticoid receptors as well as aldosterone [12]. A variety of Chinese herbal medicines include licorice and, thus, have the potential to cause pseudoaldosteronism, as in the present case.

Yokukansan contains 4.5 g of licorice/7.5 g of yokukansan. Recent clinical studies have shown that yokukansan is effective in the treatment of BPSD [7–9]. Conventional treatments for BPSD, such as typical and atypical antipsychotic drugs, have various side effects, including impairment of cognitive function, somnolence, extrapyramidal symptoms, and gait disorders, and mortality is higher in elderly patients with dementia using typical or atypical antipsychotic drugs [13]. Yokukansan, therefore, represents an attractive and beneficial alternative, because it rarely causes serious side effects [7, 8]. However, as reported previously, hypokalemia is an important side effect, with an incidence rate of 6.6 % for yokukansan,

compared with 33 % for shosaiko-to and shakuyaku-kanzo-to, respectively [14, 15]. The incidence of hypokalemia depends on the daily dose of ingested licorice and the duration of the treatment, and its precise incidence, thus, remains undetermined. Although only premature atrial contractions and electrical findings related to hypokalemia were observed in the present case, the patient showed severe hypokalemia that can lead to lethal arrhythmia. Additionally, the numbers of patients with Alzheimer's disease are increasing as the social structure ages, and more elderly Japanese patients are, therefore, likely to be treated with yokukansan for BPSD, associated with the potential danger of developing pseudoaldosteronism. Physicians should, therefore, be aware of the potential of yokukansan to induce pseudoaldosteronism, and should monitor serum K and Cl levels closely to ensure that the signs of pseudoaldosteronism are not overlooked, especially in elderly patients.

Importantly, the current patient also developed respiratory acidosis related to hypokalemia. Metabolic alkalosis is usually accompanied by respiratory compensation to mitigate alkalosis; hypoventilation followed by hypercapnia decreases the blood pH level. However, the upper limit of PaCO₂ in response to metabolic alkalosis is reported to be lower than 60 mmHg, while PaCO₂ in the present case was 60.5 mmHg, with a maximum of 61.5 mmHg on the second hospital day. The value of PaCO₂ could, thus, not be explained by simple respiratory compensation in response to metabolic alkalosis. Furthermore, the patient suffered from hypoventilation, probably related to respiratory muscle weakness, which was aggravated by sustained and severe hypokalemia. These results suggest that the patient developed both metabolic alkalosis and respiratory acidosis. This case, thus, emphasizes the importance of considering a combined acid–base disorder in patients with pseudoaldosteronism and severe hypokalemia.

It remains unclear as to why only a limited number of cases develop pseudoaldosteronism, even though many people use Chinese herbal medicines containing licorice. The development of pseudoaldosteronism may depend on various factors. Recent clinical studies have revealed that hypertension, old age, and dosing period are risk factors for developing licorice-induced pseudoaldosteronism [16, 17]. Fujiwara et al. [18] reported that the daily dose of glycyrrhizin which induces pseudoaldosteronism ranges from 20 to 586 mg, and the reported duration from 6 days to 15 years, showing a great variation in the sensitivity of the mineralocorticoid regulation system. Yasue et al. [5] also reported the possibility that concomitant inflammation can aggravate pseudoaldosteronism through endogenous cortisol production. In the present case, the patient was very elderly, and the duration of yokukansan use was 6 months. Besides, she developed urinary tract infection at the time of admission. These concomitant conditions in the present

case might have promoted the development of pseudoaldosteronism. Hence, further large-scale studies are required to investigate the factors that facilitate the development of pseudoaldosteronism.

Complications related to yokukansan use range from mild to fatal, and side effects include muscle weakness, paralytic ileus, polyuria, and rhabdomyolysis. As in the present case, constipation may be a mild side effect related to yokukansan treatment, attributable to hypokalemia-induced hypoactive bowel. More recently, the Ministry of Health, Labour and Wealth (Japan) has reported several cases of severe liver dysfunction and lethal interstitial pneumonia, and has recommended the careful use of yokukansan. Hence, although yokukansan is safe in most cases, it should be used with caution, and patients should be monitored carefully for possible complications.

In summary, we present here the case of an elderly patient treated with yokukansan, a Chinese herbal medicine containing licorice, who developed pseudoaldosteronism presenting as severe hypokalemia, metabolic alkalosis, and respiratory acidosis. Yokukansan can induce pseudoaldosteronism by inhibiting endogenous 11 β -HSD2, and nephrologists should, thus, consider the potential involvement of this drug when they encounter hypokalemic elderly patients with dementia, in order to avoid serious complications such as lethal arrhythmia and cardiac failure.

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