Case Study

Shakuyaku-kanzo-to Induces Pseudoaldosteronism Characterized by Hypokalemia, Rhabdomyolysis, Metabolic Alkalosis with Respiratory Compensation, and Increased Urinary Cortisol Levels

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Abstract

Background: Licorice, the primary ingredient of the Japanese herbal medicine shakuyaku-kanzo-to, can cause pseudoaldosteronism. Thus, shakuyaku-kanzo-to can cause this condition.

Case description: A 79-year-old woman was brought to the emergency room. She had been experiencing general fatigue, numbness in the hands, and weakness in the lower limbs and could not stand up without assistance. She presented with hypokalemia (potassium level, 1.7 mEq/L), increased urinary excretion of potassium (fractional excretion of K, 21.2%), abnormalities on an electrocardiogram (flat T waves in II, III, AVF, and V1-6), rhabdomyolysis (creatine kinase level, 28,376 U/L), myopathy, metabolic alkalosis with respiratory compensation (O2 flow rate, 2 L/min; pH, 7.473; pCO2, 61.0 mm Hg; pO2, 78.0 mm Hg; HCO3, 44.1 mmol/L), hypertension (174/93 mm Hg), hyperglycemia (blood glucose level, 200–300 mg/dL), frequent urination, suppressed plasma renin activity (0.1 ng/mL/hour), decreased aldosterone levels (2.6 ng/dL), and increased urinary cortisol levels (600.6 μg/day; reference range, 26.0–187.0 μg/day).

Conclusions: In this case, the observed reduction in the urinary cortisol levels, from 600.6 to 37.8 μg/day, led to a definitive diagnosis of pseudoaldosteronism instead of the apparent mineralocorticoid excess syndrome. Discontinuing shakuyaku-kanzo-to treatment and administering spironolactone and potassium proved effective in improving the patient’s condition. Medical practitioners prescribing shakuyaku-kanzo-to should take into account the association between licorice, which is its main ingredient, and pseudoaldosteronism.

Introduction

Licorice-induced pseudoaldosteronism, first reported in 1968, is characterized by suppressed plasma renin activity, reduced aldosterone secretion, hypertension, and hypokalemia.1 Aldosterone combines with mineralocorticoid receptors in the urineiferous tubules to exert its effects, causing sodium retention and potassium and hydrogen excretion. Similarly, cortisol can combine with mineralocorticoid receptors and exert these effects on electrolyte. However, 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), which is expressed in the renal tubular epithelial cells, dehydrates cortisol to cortisone. Cortisone is inactive and does not combine with mineralocorticoid receptors. Therefore, the mineralocorticoid effects of cortisol are not so evident under normal conditions.2,3 Glycyrrhizin (GL), a component of licorice roots, is metabolized to glycyrrhetinic acid (GA), which exerts an inhibitory effect on HSD11B2. Thus, in the presence of GA, cortisol is not dehydrated to cortisone in the urineiferous tubules, and a large amount of cortisol becomes available to combine with the mineralocorticoid receptors. This causes an increase in the mineralocorticoid effects of cortisol and a
consequent decrease in the plasma renin activity and aldosterone levels. This condition is known as pseudoaldosteronism. In this condition, the cortisol level in the blood remains within the normal range, while that in the urine increases because the conversion of cortisol to cortisone in the urinary tubules is attenuated. Shakuyaku-kanzo-to is an herbal medicine used to treat muscle cramps. It consists of galenicals derived from two plants: *Paonia lactiflora* (peony; *shakuyaku* in Japanese) and *Glycyrrhiza uralensis* (licorice; *kanzo* in Japanese). According to a previous report, the GL content of licorice is 1.00–5.51%. However, for medical use in Japan, the GL content of licorice must be at least 2.5%; no upper limit has been defined. Thus, 1.0 g of licorice used for medical purposes contains approximately 25–55 mg of GL.

In Japan, doctors are permitted to prescribe herbal medicines to patients. Shakuyaku-kanzo-to comprises 6 g of peony and 6 g of licorice; thus, it contains 150–330 mg of GL. Most doctors prescribe herbal medicines in the form of the herb extract products. TJ-68 (Tsumura & Co., Tokyo, Japan) is one of the extract products of Shakuyaku-kanzo-to. During the manufacture of extract products, 70% or more of the original herb ingredients must be retained. Thus, TJ-68 contains 105–231 mg of GL, and it is prescribed at a dose of 7.5 g daily. In Japan, it is mandatory that medicines containing 100 mg or more of GL be marketed with an accompanying statement alerting consumers to the possibility of pseudoaldosteronism. The fact that both shakuyaku-kanzo-to and TJ-68 contain more than 100 mg of GL implies that either of these agents can cause pseudoaldosteronism.

**Case Description**

A 79-year-old woman was brought to the emergency room of our hospital at the end of May 2008. She presented with general fatigue, numbness in the hands, and muscle weakness in the lower limbs and could not stand up without assistance. In 2000, her family physician had prescribed TJ-68 at a dose of 5.0 g daily, which contains 70–154 mg of GL, for muscle cramps in the lower limbs. Since the patient’s symptoms improved with this treatment, she continued to take the medicine. In 2003, she began to take 20 mg of nifedipine (Adalat Retard) daily to treat hypertension. At the end of March 2008, her husband died, after which she got depressed and lost her appetite. Her body weight decreased, but she did not have a cough and was not passing abnormal stools. In April 2008, she began to urinate frequently, and propiverine hydrochloride was prescribed at a dose of 5 mg daily for this symptom. No diuretics or other medications were used.

At the end of May 2008, the patient experienced general fatigue, numbness in the hands, and muscle weakness in the lower limbs. She was no longer able to stand up without assistance. Therefore, she was brought to the emergency room.

On physical examination, the patient’s blood pressure was 174/93 mm Hg; pulse, 68 beats/min with occasional arrhythmia; and body temperature, 37.1°C. No lung rale or cardiac murmur was heard. There was no edema in the legs. A manual muscle test revealed grades of 3–4 for the distal upper limbs and proximal lower limbs, with no laterality. The patient experienced spontaneous and grasp pain in both femurs. The deep tendon reflex was impaired at all the sites. The rest of the examinations revealed normal findings.

Chest radiography was performed, and the findings were normal. An electrocardiogram showed a sinus rhythm with occasional ventricular extrasystole; flat T waves in leads II, III, AVF, and V1-6; no long QT interval; and no U waves. Computed tomography performed for the chest and abdomen yielded normal findings, and the adrenal glands were not swollen.

Laboratory examination of the patient’s biological samples (Table 1) revealed several abnormalities, including hypokalemia (potassium level, 1.7 mEq/L), increased urinary excretion of potassium (fractional excretion of K, 21.2%), metabolic alkalosis (ambient conditions; pH, 7.539; pco2, 43.9 mm Hg; po2, 73.7 mm Hg; HCO3, 37.4 mmol/L; base excess (BE), 13.0 mmol/L), elevated creatine kinase (CK) levels (3,585 U/L), and occult blood in the urine (2+). The red blood cell count in the urine was not elevated (<1 cell per high-power field).

An endocrine analysis (Table 1) revealed suppressed plasma renin activity (0.1 ng/mL/hour [reference range, 0.1–2.0 ng/mL/hour]), decreased aldosterone levels (2.6 ng/dL [reference range, 3.6–24.0 ng/dL/hour]), and increased urinary cortisol levels (600.6 μg/day [reference range, 26.0–187.0 μg/day]).

On the basis of the patient’s history of TJ-68 treatment and the results of the laboratory examination, we considered pseudoaldosteronism induced by shakuyaku-kanzo-to as a potential diagnosis. Another suspected diagnosis was the apparent mineralocorticoid excess (AME) syndrome. This syndrome is caused by a mutation that inactivates the HSD11B2 gene; thus, the condition is characterized by persistent elevated urinary levels of cortisol. In patients for whom these two differential diagnoses are considered, a diagnosis of pseudoaldosteronism induced by shakuyaku-kanzo-to can be established if discontinuing TJ-68 treatment ameliorates the physiological abnormalities, including the elevated urinary cortisol levels. However, if discontinuing the treatment does not have this effect, a diagnosis of the AME syndrome can be established.

We requested our patient to discontinue TJ-68 intake and prescribed oral spironolactone at a dose of 50 mg daily in order to prevent cortisol from combining with the mineralocorticoid receptors and thereby improve pseudoaldosteronism. In addition, we administered intravenous (60 mEq/day) and oral (10.8 mEq/day) potassium to improve hypokalemia and prevent exacerbation of rhabdomyolysis. We adopted this treatment strategy after consulting the severe adverse effect disease treatment manual; pseudoaldosteronism, published in 2006 by the Japan Ministry of Health, Labour and Welfare.

Despite these attempts, the patient’s condition was exacerbated within the first few days of treatment (Table 1). Blood gas analysis (O2 flow rate, 2 L/min) revealed a deterioration in the patient’s condition, with the following values: pH, 7.437; pco2, 61.0 mm Hg; po2, 78.0 mm Hg; HCO3, 44.1 mmol/L; and BE, 16.6 mmol/L. These values indicated that the patient had metabolic alkalosis with respiratory compensation. Rhabdomyolysis had progressed, as was evidenced by the following values: CK, 28,376 U/L; aldolase, 264.7 U/L (reference range, 2.7–7.5 U/L); myoglobin, 8,298 ng/mL (reference range, <60 ng/mL); and urinary myoglobin, 68,000 ng/mL (reference range, 0–10 ng/mL). We administered an intravenous drip to prevent renal failure.
SHAKUYAKU-KANZO-TO INDUCES PSEUDOALDOSTERONISM

After these interventions, the patient’s condition improved (Table 1). The electrolyte and CK levels, the results of the manual muscle test and blood gas analysis, and the status of hypertension and hyperglycemia returned to normal. An electrocardiogram showed that the flat T waves in II, III, AVF, and V1-6 had improved. The symptom of frequent urination, which was present before hospitalization, disappeared after the urinary catheter was removed.

Further, the results of the endocrine analysis were improved during the hospitalization period of 17 days (Table 1). In particular, the urinary cortisol level dramatically decreased to within the normal range (from 600.6 to 37.8 µg/day; reference range, 26.0–187.0 µg/day); such a reduction would not have been noted in the AME syndrome. Thus, we established a diagnosis of pseudoaldosteronism induced by shakuyaku-kanzo-to.

Cortisol metabolism and the renin–angiotensin system, if inhibited, require 14 days and 4 months, respectively, to be restored to normal range. Therefore, renin and aldosterone levels are not useful diagnostic markers for distinguishing licorice-induced pseudoaldosteronism from the AME syndrome within 17 days. Instead, we think that the variations in the urinary cortisol levels could serve as a useful diagnostic marker for this purpose.

The patient was treated with spironolactone and potassium for 10 days. Thereafter, she regained the ability to walk without assistance and was discharged within 17 days, without any prescription.

Table 1. Progression of Laboratory Examinations

<table>
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<th></th>
<th>Admission</th>
<th>Worst</th>
<th>Discharge</th>
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<tbody>
<tr>
<td><strong>Urine analysis</strong></td>
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<tr>
<td>Sugar</td>
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<td>(-)</td>
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<tr>
<td>Protein</td>
<td>(2+)</td>
<td>(3+)</td>
<td>(-)</td>
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<td>Total protein (g/dL)</td>
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<td>Albumin (g/dL)</td>
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<td>HCO₃ (mmol/L)</td>
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<td>ACTH (pg/mL)</td>
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<td>Cortisol (µg/dL)</td>
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<td>DHEA-S (ng/mL)</td>
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<td>Urine 17-OHCS (µg/day)</td>
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<tr>
<td>Urine aldosterone</td>
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<td>0.8</td>
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HPF, high-power field; FENa; fraction excretion of Na; FEK; fraction excretion of K; cCa; corrected calcium; MB, muscle brain; ACTH; adrenocorticotropic hormone; PRA; plasma renin activity; DHEA-S; dehydroepiandrosterone sulfate; 17-OHCS, 17-hydroxycorticosteroid; 17-KS, 17-ketosteroids. ( ) indicates each unit. Reference values: FENa, 1.0–2.0, FEK, 10–20; urine myoglobin, 0–10; aldolase, 2.7–7.5; myoglobin, <60; ACTH, 9.0–52.0; cortisol, 4.5–21.1; PRA, 0.1–2.0; aldosterone, 3.6–24.0; DHEA-S, 70–1,770; urine cortisol, 26.0–187.0; urine 17-OHCS, 2.2–7.3; urine 17-KS, 2.4–11.0; urine aldosterone, 0.0–7.5.

Discussion

Here, we report the case of a patient with severe pseudoaldosteronism induced by shakuyaku-kanzo-to, presenting with hypokalemia, increased urinary potassium excretion, abnormalities on an electrocardiogram, rhabdomyolysis, myopathy, metabolic alkalosis with respiratory compensation, hypertension, hyperglycemia, frequent urination, suppressed plasma renin activity, decreased aldosterone levels, and increased urinary cortisol levels.

In this case, the observed reduction in the urinary cortisol levels, from 600.6 to 37.8 µg/day, led to a definitive diagnosis of pseudoaldosteronism instead of the AME syndrome. Discontinuing shakuyaku-kanzo-to treatment and administering spironolactone and potassium proved effective in improving the patient’s condition. Medical practitioners prescribing shakuyaku-kanzo-to should take into account the association between licorice, which is its main ingredient, and pseudoaldosteronism.

We considered that our patient developed rhabdomyolysis because of hypokalemia. A case of licorice-induced hypokalemic rhabdomyolysis with acute renal failure, found on autopsy, has been reported.12 In the autopsy case, severe rhabdomyolysis had occurred because of hypokalemia (potassium level, 1.9 mEq/L). Considering this and the fact that our patient’s potassium level was 1.7 mEq/L at the time of admission, we can presume that if she had visited our hospital after a longer delay, more severe rhabdomyolysis and fatal renal failure might have occurred.

We considered that pseudoaldosteronism induced metabolic alkalosis in our patient. In pseudoaldosteronism, the urinary excretion of both potassium and hydrogen is accelerated. Moreover, alkalosis can cause hypokalemia and vice
versa. The fact that our patient’s condition did not respond to treatment within the first few days may be attributable to this complex interaction.

Our patient had been under treatment with nifedipine for hypertension, and her blood pressure was 174/93 mm Hg at the time of admission. However, it was normalized by the time of discharge, without any medication. Considering this and the fact that she developed hypertension after prolonged treatment with shakuyaku-kanzo-to, we thought that her hypertension might have been induced by pseudoaldosteronism.

During the first few days of hospitalization, the patient’s blood glucose levels were approximately 200–300 mg/dL, but they were normalized by the time she was discharged. It is possible that the elevated blood glucose levels were due to hypokalemia-induced failure of insulin secretion.

Before admission to our hospital, the patient had been urinating frequently and had been prescribed propiverine hydrochloride. However, this symptom had disappeared by the time of discharge, without any medication. The frequent urination may have been related to hypokalemia-induced polyuria.

Although the patient had taken shakuyaku-kanzo-to for 8 years, pseudoaldosteronism was not manifested until the time of admission to our hospital. The manifestation of this condition may have been related to her husband’s death, which occurred 2 months before the admission. She used to live happily with her husband but went into depression after he died; this probably triggered an increase in her adrenocorticotropic hormone and cortisol levels. Consequently, more cortisol became available to combine with the mineralocorticoid receptors, and this exacerbated the pseudoaldosteronism. The situation was worsened by the fact that the patient lost her appetite after her husband died; thus, it can be assumed that her potassium intake decreased. We speculate that this led to the development of pseudoaldosteronism with hypokalemia. In addition, as stated in the Introduction, there is no upper limit on the permissible GL content in licorice used for medical purposes in Japan; therefore, the licorice in TJ-68 may contain a large amount of GL. Variations in the GL content within a single product may be associated with the development of pseudoaldosteronism.

It has been reported that the sensitivity of the body to GL differs among individuals. In this previous study, GL at a dose of 546 mg/day was prescribed for 4 weeks to 12 patients with chronic hepatitis. This treatment caused pseudoaldosteronism in 5 of these patients but did not affect the other 7. However, the reason for this discrepancy in the observations could not be identified.

Sodium retention associated with licorice consumption has been thought to be due to a direct mineralocorticoid effect exerted by GA. However, in 1987, this condition was shown to be associated with significant changes in the metabolism of cortisol; these changes reflected inhibition of HSD11B2. Thus far, GA, the primary metabolite of GL, has been shown to cause licorice-induced pseudoaldosteronism and is known to inhibit the activity of HSD11B2.

One study has also reported that 3- beta-d-(monoglucuron Id)18β-glycyrrhetinic acid (3MGA), another metabolite of GL, causes licorice-induced pseudoaldosteronism. Instead, much 3MGA was observed in the patients with pseudoaldosteronism. Furthermore, 3MGA was shown to inhibit HSD11B2.

From the viewpoint of pharmacokinetics, it has been reported that elevated blood concentrations of 3MGA are maintained by repeated administration of GL, while the concentrations of GA and GL showed no difference. In addition, 3MGA administration is reported to decrease the plasma potassium levels. Therefore, it has been documented that 3MGA accumulation may be involved in the pathogenesis of licorice-induced pseudoaldosteronism. Moreover, the plasma concentration and urinary excretion of GL and 3MGA were found to be markedly elevated in rats with liver dysfunction as compared to normal rats; however, the GA levels were not affected by oral GL administration. It has also been suggested that 3MGA is secreted into the bile via the hepatic multidrug resistance-associated protein (Mrp)-2 and that its dysfunction would reduce 3MGA clearance in conditions such as liver dysfunction. Since 3MGA accumulation in the liver causes an increase in its excretion through the renal tubules, this agent is considered to be related to the pathogenesis of pseudoaldosteronism.

According to the nucleotide polymorphism database dbSNP, the HSD11B2 gene exhibits approximately 100 polymorphisms. These polymorphisms probably determine an individual’s sensitivity to shakuyaku-kanzo-to or GL, depending on the dosage or duration of treatment.

Licorice has been proven to have antioxidant properties. Therefore, the use of herbal medicines containing this ingredient may increase in the future. To ensure the safe application of herbal medicines containing licorice, further studies on the associated gene–environment interactions are required.

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Disclosure Statement

No competing financial interests exist.

References


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