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CASE REPORT

LICORICE-INDUCED APPARENT MINERALOCORTICOID EXCESS CAUSING PERSISTENT HYPERTENSION AND HYPOKALEMIA

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Abstract

Chronic ingestion of licorice is known to cause numerous metabolic and electrolyte disturbances. Severe hyponatremia, hypertension, and hypokalemia as well as metabolic alkalosis are amongst the most common consequences of chronic ingestion resulting in an apparent mineralocorticoid excess (AME). Treatment predominantly consists of cessation of licorice ingestion, potassium replenishment and aldosterone antagonists. Given the potentially lethal effects of chronic licorice ingestion, clinicians should be made aware of the presentation of AME and the proper management. We present the rare case of a 62-year-old male with licorice-induced apparent mineralocorticoid excess secondary to excessive licorice tea intake. Initial presentation included severe hypokalemia of 2.2mmol/L and hypertension of 180/110mmHg, while eunatremic (Na, 144meq/L).

Keywords: Licorice, tea, Glycyrrhizic acid, cortisol, apparent mineralocorticoid excess.

INTRODUCTION

Chronic ingestion of licorice may mimic the renin-aldosterone system resulting in sodium and water retention, hypokalemia, hypertension, and metabolic alkalosis. Glycyrrhizic acid, the active component of licorice, inhibits the enzyme 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone(1). High levels of plasma cortisol stimulate the mineralocorticoid receptors in the renal distal tubules and collecting ducts resulting in the syndrome of apparent mineralocorticoid excess (AME), characterized by resistant hypertension, hypokalemia, hypernatremia, metabolic alkalosis, as well as low plasma renin and aldosterone levels (2). Farese *et al.* proposed that the plasma half-life of cortisol is prolonged due to increased amounts of unconjugated cortisol metabolites relative to total cortisol metabolites in the urine, suggesting that licorice does impair normal cortisol metabolism (2). Treatment of this paradigm has consisted of discontinuation of licorice ingestion, potassium supplementation, and short-term use of aldosterone antagonists. It should be noted that this diagnosis is significantly less common than other causes of hypokalemia and hypertension, therefore requiring careful patient questioning. Licorice in all forms, including tea, is readily available online and marketed as a weight-loss aid, treatment for the common cold, flu, and gastrointestinal issues. Licorice is known to be consumed as a candy, and most manufacturers have removed the active component glycyrrhizin to avoid the harmful side effects. However, there is little public awareness about the complications of excessive intake of licorice extract tea, raising more of a concern due to the widespread variety of concentrations available to consumers. Clinicians should be aware of the effects of such non-FDA approved over-the-counter and dietary supplements in order to guide treatment and avoid prescribing cascades. We present the rare case of licorice induced AME due to chronic ingestion of licorice extract tea.

CASE PRESENTATION

A 62-year-old man presented to the emergency room secondary to bilateral upper extremity numbness and tingling in the chest which radiated to the chin. The patient stated these symptoms lasted for about five minutes and repeated about 3-4 times. Prior to arrival in the emergency room, the patient was seen at an urgent care clinic, where his blood pressure was found to be elevated at 180/100. The patient's past medical history consisted of benign prostate hyperplasia and carpel tunnel syndrome with no history of hypertension. On admission, the patient had a serum sodium of 144mEq/L, serum potassium of 2.2 mEq/L, serum phosphorus of 1.9 mg/dL and bicarbonate of 34units. Clinical examination and chest X-ray were

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unremarkable. The patient also stated that he had been drinking licorice tea for the past 3-4 months. More recently, he was also drinking a new preparation of licorice tea that was more concentrated. He stated that his usual intake was at least two large cups daily. His medication history included alfuzosin extended release 10 mg once daily and omeprazole 40 mg once daily.

Laboratory work-up and management

The initial differential diagnosis included licorice-induced AME, primary hyperaldosteronism, an adrenal adenoma, or renal artery stenosis. Primary aldosteronism was ruled out since aldosterone levels were nearly undetectable at < 1 ng/dL, as well as the renin activity level at < 0.167 ng/mL/hr. Twenty-four-hour urine aldosterone levels were also low at <2.5 ng/mL and CT scans of the abdomen/pelvis were unremarkable. Due to the patient's history of ingesting licorice tea, as well as his symptoms and initial lab work, the diagnosis of licorice-induced AME was established. The patient was initially treated with large doses of intravenous potassium and phosphate supplementation for electrolyte repletion and intravenous hydralazine to acutely control his blood pressure. The following day the patient developed persistent nausea and vomiting, which was uncontrolled with intravenous ondansetron. Metoclopramide and fluids with potassium were added to the regimen and symptoms resolved the following day. At this point the patient had persistent, severe hypokalemia and hypertension despite large doses of intravenous potassium and hydralazine, requiring admission to the intensive care unit. The patient presented eunatremic with a sodium of 144mEq/L and his sodium remained within normal limits throughout his stay in the hospital. Three days later the patient's potassium normalized to 3.7 mEq/L and blood pressure reduced to 121/73 (Table 1). The patient was advised to stop drinking licorice tea or ingest any type of licorice and was discharged on oral potassium 20 mEq twice daily, spironolactone 50 mg twice daily, and hydralazine 25 mg tablets three times daily. The patient was scheduled for a follow-up appointment one week after discharge for monitoring and adjustment of medications. During his follow-up, his potassium levels and blood pressure were stabilized, and his potassium, spironolactone and hydralazine were discontinued.

DISCUSSION

Licorice-induced mineralocorticoid excess is a rare phenomenon with only a limited number of cases reported in the literature. Symptoms of licorice-induced mineralocorticoid excess may also mimic other genetic causes including Liddle's syndrome, characterized by a defect in the epithelial sodium channel resulting in increased sodium absorption and potassium wasting. Deficiencies in 11β-hydroxysteroid dehydrogenase enzyme type 2 caused by an autosomal recessive mutation can also cause a rare form of juvenile hypertension characterized by low birth weight, failure to thrive, and renal failure (3). In our patient, it was that the associated symptoms and relative lab work-up were consistent with chronic licorice ingestion from extract tea. There is limited data on the effects of the renin-aldosterone system after cessation of licorice. Farese *et al.* reported that the renin-aldosterone system was suppressed for nearly four months following cessation after a patient ingested 60-100 grams of licorice daily for four to five years (2). In our patient, potassium levels remained consistently low for three days with potassium treatment, and began to normalize after spironolactone treatment was added. This suggests a slight response to spironolactone treatment on the renin-aldosterone system. Little is known about the quantity and duration of licorice ingestion needed to have such a profound inhibitory effect on 11β-hydroxysteroid dehydrogenase type 2 enzyme; however, it has been reported that the enzyme can be suppressed for two weeks after licorice discontinuation, with lasting suppressive effects on the renin-aldosterone system for several months. The effect of licorice on blood pressure has been described as a linear dose-response relationship (4–6). This explains our patient's severe persistent hypertension due to his extensive prolonged licorice consumption for several months.

Table 1. Potassium and blood pressure monitoring during patients length of stay

Days since Admission	Average K+ levels (mmol/L)	Average Blood Pressure (mmHg)
1	2.2	180/100
2	2.1	158/89
3	2.5	155/103
4	3.3	146/96
5	3	160/133
6	3.7	135/78

In 2017, the US Food and Drug Administration published a warning prior to Halloween about the negative consequence of licorice ingestion, including abnormal heart rhythms, high blood pressure and hypokalemia (7). Although many licorice or licorice-flavored products manufactured in the United States do not actually contain glycyrrhizic acid, it is important to note that licorice-extract tea is still widely available for purchase through major online retailers. Many of these licorice tea brands do not explicitly warn about the side effects of licorice, and some go further to advocate for a "stronger tea" stating to use two tea bags. Most licorice teas also contain a variety of other herbs and spices, therefore making it harder to quantify the actual amount of licorice in each tea bag. The FDA assumes that 0.15% glycyrrhizin in non-alcoholic beverages is the maximum allowable level that is considered safe (8). In a survey of 33 brands of licorice tea, the mean glycyrrhizin content was found to be 126 mg/L (range 2-460 mg/L). A regular size 250 mL cup of licorice tea could be expected to contain, on average, around 31.5 mg of glycyrrhizin (9). However, licorice extract teas that are not manufactured in the United States may have considerably higher levels of glycyrrhizin. The severity of symptoms and prolonged adverse effects associated with licorice toxicity warrants further investigation of licorice's effects on 11β-hydroxysteroid dehydrogenase activity, as well as increased awareness of the potential dangers of such unregulated products.

Clinicians should be made aware of the consequences of extreme or abnormal dietary habits such as licorice-induced apparent mineralocorticoid excess. A thorough dietary history should be taken to ensure proper levels of ingestion of even routine ingredients such as licorice. We present the case of licorice-induced AME due to excessive consumption of licorice secondary to increased tea intake.

Conflict of interest

The authors declare that they have no conflict of interest.

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