Hypertensive emergency induced by licorice tea

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An 84-year-old man presented to the emergency department with a hypertensive emergency. He reported a 1-week history of persistently elevated measurements, taken at home, of systolic blood pressure (between 180 and 210 mm Hg), along with symptoms of headache, photophobia, chest pain and fatigue. On presentation to the emergency department, his blood pressure was 196/66 mm Hg. He had signs of volume overload on physical examination, including pulmonary crackles on auscultation and pitting edema of the lower extremities up to the knees. Chest radiography was consistent with mild pulmonary edema.

The patient's initial laboratory results in the emergency department showed a low potassium level of 2.5 (reference range 3.5–5.0) mmol/L, an elevated bicarbonate level of 31 (reference range 23–29) mmol/L and an increased troponin level of 0.14 (upper limit of normal 0.04) μg/L, with no signs of myocardial ischemia on the electrocardiogram.

The patient had long-standing hypertension. A blood pressure measurement taken 4 months earlier showed adequate control (125/60 mm Hg). He also had a history of coronary artery disease, type 2 diabetes and dyslipidemia. His medications included irbesartan, hydrochlorothiazide, acetylsalicylic acid, metformin, empagliflozin, insulin, ezetimibe and atorvastatin. He took furosemide on alternating days for mild venous insufficiency causing pitting edema of the feet.

On admission, the patient was started on a combination of amlodipine, metoprolol and hydralazine. Irbesartan was initially held to avoid altering tests of endocrine biochemistry and later resumed. Hydrochlorothiazide was held until the end of his hospital stay to avoid aggravating the hypokalemia. The patient's presenting symptoms resolved over the next 24 hours, except for orthopnea and paroxysmal nocturnal dyspnea, which improved after several days of diuresis with intravenous furosemide.

On further questioning, the patient volunteered that he had been ingesting 1 to 2 glasses of homemade licorice root extract called "erk sous" daily for the 2 weeks leading up to his presentation. Although he knew of the potential association between licorice consumption and high blood pressure, he did not think of it when he noticed his blood pressure starting to rise.

Screening for pheochromocytoma and Cushing syndrome was negative. Plasma renin activity (0.01 ng/L/s; reference range 0.45–2.06 ng/L/s) and serum aldosterone (71 pmol/L; reference range 111–860 pmol/L) were both suppressed, confirming a state of pseudohyperaldosteronism. We diagnosed licorice-induced pseudohyperaldosteronism.

KEY POINTS

- Licorice-induced pseudohyperaldosteronism is an unusual but important cause of hypertensive emergency.
- Common findings of licorice-induced pseudohyperaldosteronism include signs of sodium retention, such as hypertension, hypokalemia or metabolic alkalosis, with low serum aldosterone levels.
- Given Canada's multicultural population, physicians should consider screening for licorice root intake in patients with difficult-to-control hypertension.

With complete abstinence from licorice extract while he was in hospital, the patient's blood pressure gradually improved and was 140/80 mm Hg on discharge from the hospital 13 days after presentation. He was sent home on amlodipine, metoprolol, irbesartan, hydrochlorothiazide and a taper of furosemide, along with the remainder of his usual medications.

The patient was seen in clinic 3 weeks later; his blood pressure was 110/57 mm Hg and he felt well. He had not taken any licorice extract since his hospital admission. Metoprolol and amlodipine were stopped. His potassium level was normal (3.8 mmol/L). The patient's renin activity level was 3.81 ng/L/s and his aldosterone level was 300 pmol/L, indicating complete resolution of the pseudohyperaldosteronism. Cortisone assays were not available.

Discussion

Licorice, the root of the plant *Glycyrrhiza glabra*, has been used for thousands of years for its therapeutic properties and as an essential ingredient to various sweets and beverages. Its use can be traced back to ancient Assyria, Egypt, China and India.[1] To this day, it remains popular in the Middle East, as well as several parts of Europe. Erk sous is a popular Egyptian drink, sought after for its thirst-quenching effect, especially during the month of Ramadan. It is traditionally prepared by combining licorice root and baking soda in a cloth and adding water to it drop by drop over several hours.

Licorice is well known to exacerbate high blood pressure in patients with hypertension. Less commonly, licorice has been shown to cause *de novo* hypertension in previously unaffected individuals.[2] Several cases of licorice-induced hypertensive crises have been reported, with various presentations including heart failure with pulmonary edema, hypertensive encephalopathy and stroke. Other important adverse effects include hypokalemic myopathy, rhabdomyolysis and cardiac arrhythmia.[3]

The adverse effects of licorice are primarily a consequence of the hypertension, volume expansion and hypokalemia that result from excessive mineralocorticoid receptor activation. Mineralocorticoid receptors are nonselective and bind equally to both the mineralocorticoid hormone aldosterone and to the glucocorticoid hormone cortisol. Cortisol, however, circulates in the blood in concentrations 3 orders of magnitude greater than aldosterone and must be converted into its inactive metabolite, cortisone, to prevent excessive activation of the mineralocorticoid receptors. The conversion of cortisol into cortisone is mediated by 11-β-hydroxysteroid dehydrogenase type 2 (11-β-HSD2) in the distal tubules of the kidney.[4]

In licorice intoxication, the 11-β-HSD2 enzyme is inhibited by glycyrrhizic acid and glycyrrhetinic acid, which are the main active metabolites of licorice.[5] These metabolites are derivatives of glycyrrhizin, which is the same compound that gives licorice its characteristic sweet taste.[4] Inhibition of 11-β-HSD2 by glycyrrhizin metabolites leads to impaired inactivation of cortisol into cortisone, which results in excessive activation of the mineralocorticoid receptors.

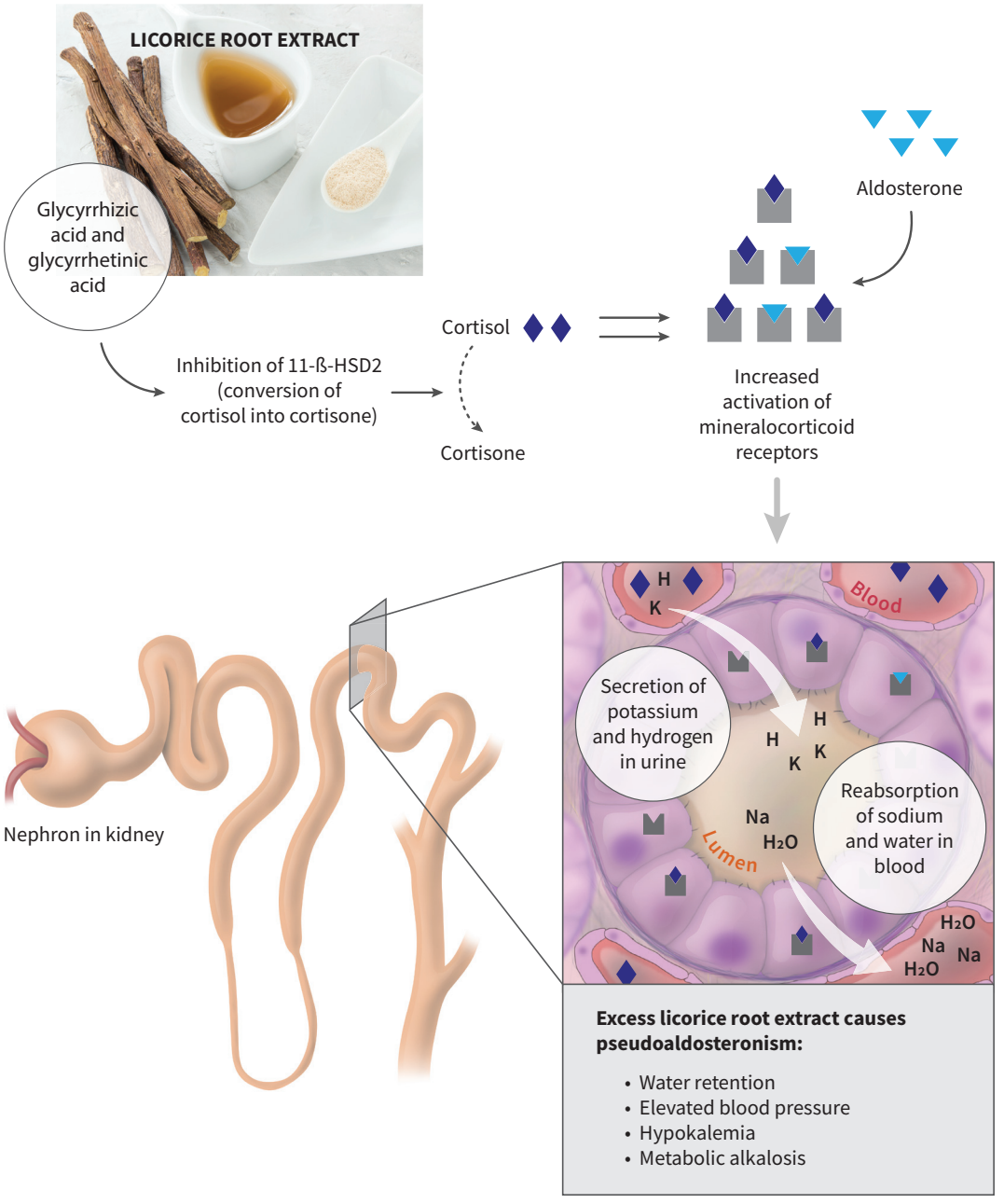

Figure 1: Demonstration of the main mechanism of action of licorice through inhibition of 11-β-hydroxysteroid dehydrogenase type 2 (11-β-HSD2) in the distal tubules of the kidney. Note: H = hydrogen ion, H_2O = water, K = potassium, Na = sodium.

Because of the receptor activation, there is increased reabsorption of sodium and water, and loss of potassium and hydrogen ions in the urine. Clinically, this translates into volume retention with a consequent rise in blood pressure, hypokalemia and metabolic alkalosis (Figure 1). The effect on blood pressure begins as soon as 1 week after daily ingestion and peaks at around 2 weeks.[6]

Licorice intoxication effectively results in a state that is clinically indistinguishable from hyperaldosteronism, which is why it is termed pseudohyperaldosteronism. However, the 2 entities can be differentiated by measuring plasma renin activity and plasma aldosterone. In response to excessive stimulation of the mineralocorticoid receptors by cortisol, both plasma renin activity and aldosterone will be low in licorice-induced pseudohyperaldosteronism; in contrast, plasma aldosterone levels will be elevated in both primary and secondary hyperaldosteronism.

Other entities can also lead to low plasma renin activity and serum aldosterone, such as salt loading, without necessarily being associated with a clinical picture of hyperaldosteronism. Furthermore, licorice intoxication is not the only cause of pseudohyperaldosteronism; other causes include grapefruit intoxication, various endocrine deficiencies and genetic mutations affecting the 11-β-HSD2 enzyme or the mineralocorticoid receptor.[3] The endocrine biochemistry should therefore not be used to confirm a diagnosis of licorice-induced pseudohyperaldosteronism outside of an appropriate clinical context. Some laboratories can measure cortisone and cortisol in the urine or in venous blood, which can aid in supporting the diagnosis of licorice intoxication. As predicted by the pathophysiology of licorice intoxication, one would expect the cortisol:cortisone ratio to be markedly increased in this setting.[3]

Treatment of licorice-induced hypertensive crisis involves supportive measures aimed at reducing blood pressure until the effect of the licorice wears off. Potassium replacement may be necessary in severe cases, and potassium-sparing diuretics may be added for their mineralocorticoid antagonism.[3]

Prevention

Several countries, including the United Kingdom, impose strict rules on product labelling and require a written warning to be printed on products with high concentrations of glycyrrhizin, specifically addressed to patients with hypertension.[7] The US Food and Drug Association considers glycyrrhizin safe, if consumed in moderation, and publishes maximum allowable concentrations for various foods.[8] Health Canada, the regulatory body for food and drugs in Canada, also has an advisory that licorice should not be used if a patient has hypokalemia, high blood pressure, a kidney or cardiovascular disorder, or is taking a medication that might lead to an electrolyte imbalance.[9]

Despite existing regulations and prior knowledge of the potential adverse effects of licorice, our patient did not believe he was drinking an excessive amount of licorice. He therefore did not associate his consumption of licorice with his symptoms when they first developed. Although many regulatory bodies publish safe maximum concentrations of glycyrrhizin, the concentration of glycyrrhizin is difficult to estimate in practice, especially in homemade licorice extract like the drink produced by our patient. He did not use a Canadian product, instead bringing licorice root from Egypt to prepare his own extract at home. However, licorice-related adverse events have been reported from products obtainable in Canada. Specifically, a recent report documents a case of licorice-induced hypertension from jelly beans consumed in Canada.[10] This case relates to black licorice, which typically contains extract from the *G. glabra* plant, and not to the red licorice confectionery, which does not.[10]

The current case of hypertensive emergency secondary to licorice intoxication serves as a reminder of the importance of questioning patients on intake of licorice-containing products when they present with *de novo* hypertension, exacerbated hypertension or hypertensive crisis. Moreover, it highlights the opportunity that physicians have to educate their patients with hypertension about the potential adverse effects of licorice to prevent licorice-related complications.

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