Low-dose liquorice ingestion resulting in severe hypokalaemic paraparesis, rhabdomyolysis and nephrogenic diabetes insipidus

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Background

In daily practice hypokalaemia is frequently observed. It can be accompanied by various adverse events and can even be life threatening. Frequent causes are intestinal and urinary loss, i.e. diarrhoea or use of diuretics.

Glycyrrhizin-containing substances, such as liquorice, are a well-known but rare cause of hypokalaemia. They can induce an apparent mineralocorticoid excess-like syndrome, often accompanied by hypertension, metabolic alkalosis, sodium retention and renal potassium wasting [1].

We will discuss a case of liquorice-induced hypokalaemia causing serious electrolyte disorders and severe clinical symptoms.

Case report

Presentation

A 52-year-old Caucasian man presented to our emergency department with severe asthenia and muscle cramps. Several days before admission he noticed muscle weakness in his limbs. This gradually progressed, resulting in a fall and inability to stand. He denied nausea, vomiting, diarrhoea or use of laxatives. There were no respiratory or cardiac complaints. His daily nutritional intake predominantly consisted of soup and bread and he had abstained from consuming alcohol a few months previously.

Relevant medical history included hypercholesterolaemia and hypertension, treated with lisinopril 20 mg per day, hydrochlorothiazide 12.5 mg per day and amlodipine 5 mg per day, but with questionable therapeutic adherence. He ceased the statin therapy 1 year before admission.

Clinical examination revealed severe paraparesis with preserved sensory input and low reflexes: he was unable to lift his limbs against gravitational force. He was cachectic, with a total body weight of 44 kg at admission, a length of 166 cm and a body mass index of 16.0 kg/m². He had mild hypertension with a blood pressure of 156/103 mmHg. All other physical findings were normal.

Investigations

Laboratory investigations at admission revealed metabolic alkalosis (pH: 7.54; pCO₂: 46.4 mm Hg; HCO₃⁻: 39 mmol/L) and severe hypokalaemia (1.6 mmol/L). Nine hours later, a control sample showed further decrease of the potassium to 1.5 mmol/L, despite intravenous potassium and magnesium substitution. Urine collection revealed a high urinary potassium: 188.6 mmol/24 h (reference range (RR): 26.0–123.0). The transtubular potassium gradient (TTKG) was 10.2, indicating marked renal potassium wasting.

In addition there were arguments for rhabdomyolysis: CK levels were 118.87 μkat/L (RR: 0.83–2.84) [7118 U/L (RR: 50–170)] at admission and increased to 925.48 μkat/L (55 418 U/L) few days after admission; urinary myoglobin was 930.37 nmol/L (RR: <0) [16 300 μg/L (RR: <0)]. The kidney function remained normal during his stay.

Differential diagnosis

The key abnormalities of our case were an extreme hypokalaemia, accompanied by metabolic alkalosis, moderate hypertension, rhabdomyolysis and polyuria. Diuretic abuse was excluded through urinary sampling and our patient denied laxative abuse. Bartter and Gitelman syndrome, Liddle syndrome, congenital adrenal hyperplasia and other congenital or genetic disorders were highly unlikely in view of his age and since previous potassium levels were normal. The suppressed renin and aldosterone and normal morning cortisol suggested an apparent mineralocorticoid excess-like disorder. Other endocrinopathies, such as Cushing syndrome and ectopic corticotrophin syndrome, could be excluded through laboratory findings (Table 1). Through a careful medication and dietary history our patient disclosed the consumption of two centimetres of liquorice root a day for the last 2 months, an equivalent of 1.5 g liquorice daily.

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uted to the severity of the symptoms [11, 12].

tectable in urine sample) and anorexia may have contrib-

than others remain unclear, but possible risk factors have

suggested upper limit for ingestion.

tration of 18.0

48.5 mg of glycyrrhizin (assuming a glycyrrhizin concen-

lysis and nephrogenic diabetes insipidus on ingesting an

developed severe hypokalaemic paraparesis, rhabdomyo-

regular ingestion of 100 mg of glycyrrhizin a day is safe for

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sodium and

weakness, fatigue, hypertension, renal potassium loss,

condition which typically manifests itself with muscle

for cortisol-cortisone ratio, systolic blood pressure, fall in

pseudohyperaldosteronism. Dose

–

Morning ACTH (pmol/L) [pg/mL] 1.4 [6.2]

Morning cortisol (nmol/L) [μg/dL] 535 [19.6]

24-h urine free cortisol (nmol/d) [μg/d] 762.8 [276.0]

Table 1. Endocrine findings and urinary potassium

| Variable                  | At admission | After 1 month liquorice cessation | Reference range                      |
|---------------------------|--------------|----------------------------------|--------------------------------------|
| Aldosterone (pmol/L) [pg/mL] | <28 [<10]   | 42 [15]                          | 28–4440 [10–160] (supine)             |
| Renin (pmol/L) [pg/mL]    | 0.05 [1.9]   | 0.48 [20.2]                      | 0.06–0.52 [2.4–21.9] (supine)         |
| TSH (mU/L)                | 1.724        |                                  | 0.465–4.68                           |
| Morning ACTH (pmol/L) [pg/mL] | 1.4 [6.2]   | 265 [9.6]                        | 1.0–10.7 [4.7–48.8]                   |
| Morning cortisol (nmol/L) [μg/dL] | 535 [19.6] |                                  | 185–623 [6.7–22.6]                    |
| 24-h urine free cortisol (nmol/d) [μg/d] | 762.8 [276.0] |                                | <248.4 [>90]                         |

Other known risk factors for increased sensitivity to li-

quorice ingestion are essential hypertension, old age and

salt sensitivity [13–15]. The increased susceptibility in

chronic inflammatory conditions can be explained by sup-

pression of 11-beta-HDS2 and stimulation of ACTH secretion

by inflammatory cytokines [16]. Mutations in the 11-beta-

HDS2 enzyme can also contribute to increased liquorice

sensitivity [17]. It is unclear whether male or female sex

imposes a higher susceptibility. Some authors suggest

increased sensitivity for liquorice in females and use of

contraceptives, which may be explained by inhibition of

11-beta-HDS2 by oestrogens or through interaction with

the mineralocorticoid receptor [18]. In contrast, other

authors report the renin-angiotensin-aldosterone system

is more responsive to liquorice in men [19].

Discussion

Liquorice is made from the root of Glycyrrhiza glabra,

commonly known for its sweet flavour. Throughout history

it has been used in herbal medicine and there are even

reports of anti-inflammatory, antiviral, antimicrobial, anti-

oxidative, hepatoprotective and cardioprotective proper-

ties [2]. Nevertheless liquorice is also well known for

inducing hypertension and other health hazards.

The active component is glycyrrhizin, which inhibits

renal 11-beta-hydroxysteroid dehydrogenase type 2 (11-

beta-HDS2). This enzyme converts active cortisol to the in-

active cortisone. Hence cortisol escapes inactivation and

this leads to the characteristics of the syndrome of appar-

ent mineralocorticoid excess [1, 3].

Despite worldwide use, glycyrrhizin toxicity is a rare

condition which typically manifests itself with muscle

weakness, fatigue, hypertension, renal potassium loss,

sodium and fluid retention, metabolic alkalosis and

pseudohyperaldosteronism. Dose–response correlations

for cortisol-cortisone ratio, systolic blood pressure, fall in

plasma potassium and fluid retention have been reported

[4–7]. The onset and severity of the symptoms depend on

the dose and duration of liquorice intake, as well as indi-

vidual susceptibility [8].

The European Union states that an upper limit for

regular ingestion of 100 mg of glycyrrhizin a day is safe for

the majority of the population [9]. However our patient

developed severe hypokalaemic paraparesis, rhabdomyo-

lysis and nephrogenic diabetes insipidus on ingesting an

estimated 1.5 g of liquorice a day, which contains 27.0–

48.5 mg of glycyrrhizin (assuming a glycyrrhizin concen-

tration of 18.0–32.3 mg/g) [9, 10]. This is far below the

suggested upper limit for ingestion.

The reasons why some individuals are more susceptible

than others remain unclear, but possible risk factors have

been reported. In our case use of diuretics (though not de-

tectable in urine sample) and anorexia may have contrib-

uted to the severity of the symptoms [11, 12].

Treatment

All oral medication and liquorice ingestion was ceased. Up
to 15 mmol potassium chloride per hour was needed to

rect the hypokalaemia, which took about 3 days. Due
to persistent hypertension an ACE-inhibitor was started.

At discharge alkalosis was still present, but the kalaemia

remained within the normal range without further need for

substitution. One month after permanent cessation of the

liquorice ingestion, all ion, metabolic and endocrine dis-

orders returned to normal. This confirmed our diagnosis of

liquorice-induced apparent mineralocorticoid excess syn-

drome with hypokalaemic paraparesis, rhabdomyolysis and

nephrogenic diabetes insipidus.

Teaching points

1. Liquorice toxicity must be considered in unexplained

metabolic alkalosis or hypokalaemia and in treatment-

resistant hypertension.

2. This case demonstrates that serious adverse events are

possible even in consumption of low doses of liquorice.

3. Susceptibility is variable between individuals depending

onendo- and exogenous risk factors, such as essential

hypertension, salt sensitivity, old age, malnutrition, use of

diuretics, chronic inflammatory conditions and muta-

tions in the 11-beta-HDS2 gene. The influence of male

or female sex is unclear.

4. The effects of liquorice are reversible upon cessation.

Potassium supplentation is often necessary in hypokalae-

mic states. Addition of spironolactone or dexametha-

sone may be considered.

Conflict of interest statement. None declared.

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