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CASE REPORT

Potentially lethal sweets

S.H.G. Mensink[1], B.P. Ramakers[1], A.C. Heijckmann[2], A. Koopmans[1]

Department of [1]Intensive Care, and [2]Internal Medicine, Bernhoven Hospital, Uden, the Netherlands

Correspondence

S.H.G. Mensink - hgmensink@gmail.com

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Abstract

Excessive intake of liquorice can cause severe hypertension, hypokalaemia and metabolic alkalosis due to pseudo-hyperaldosteronism. We present here a case of excessive liquorice intake by lozenges ('Fisherman's Friend'), which was in excess of 30 times the proposed upper limit of 100 mg/day. This article emphasises the importance of taking a thorough medical history, which in this case eventually led to the correct diagnosis.

Introduction

This case underlines the importance of a thorough medical history of the patient's lifestyle. In the case of an unconscious patient, a heteroanamnesis with family and/or friends can be of similar importance.

In this patient, the combination of severe hypertension with hypokalaemia and metabolic alkalosis was suspected to be causing a disturbance in the renin-angiotensin-aldosterone system. With the main causes being primary hyperaldosteronism, secondary hyperaldosteronism (e.g. renovascular disease), and non-aldosterone mineralocorticoid excess (e.g. liquorice abuse), a thorough medical history is crucial to reach the correct diagnosis and subsequently initiate the required treatment.

Case report

A 63-year-old woman with decreased consciousness presented to the emergency department with presumed pneumonia. Medical history taken from her husband revealed that she was in a good condition in the morning and that there were no signs of depression or suicidal tendencies. Later the same day he found her unconscious. Previous medical history showed an iron deficiency anaemia. She was not on any medication except incidental ibuprofen and oxazepam. Physical examination showed a spontaneously breathing patient (15 times/min), with a blood pressure of 197/95 mmHg, pulse of 96 beats/min, a Glasgow Coma Scale of E4M4V1 with no other neurological symptoms and a temperature of 38°C. Additional physical examination showed no abnormalities.

Laboratory investigation revealed severe metabolic alkalosis, severe hypokalaemia, leucocytosis and known anaemia *(table 1/figure 1)*.

Toxicological screening for soft and hard drugs, paracetamol, lithium and digoxin was negative. A chest X-ray showed an infiltrate in the left lung and computer tomography (CT) scan showed no intracranial abnormalities. With a heart rate of 94 beats/min, the ECG showed no abnormalities except a slightly prolonged QTc interval of 476 msec.

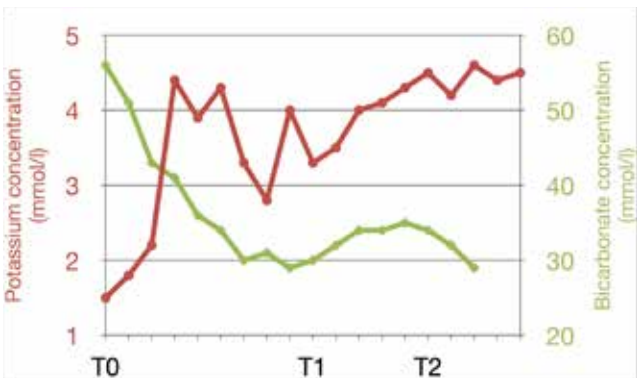

Figure 1. Changes in potassium and bicarbonate concentrations
T0= Presentation at ED/admission to ICU; T1= Post extubation; T2= Day of discharge to department of internal medicine

The patient was admitted to the intensive care unit (ICU) for further diagnostics and treatment. Antibiotic treatment (cefuroxime), potassium suppletion and blood transfusion were initiated. The following day she developed respiratory failure due to pulmonary sepsis. She was intubated and mechanically ventilated for seven days and successfully treated with spironolactone and perindopril for accelerating hypertension (220/120 mmHg).

Table 1. Laboratory results of the patient

	T0 (ED/ICU) day 0	T1 day 9	T2 day 14	Reference values	
Blood count					
Haemoglobin	4.7	6.6	6.5	7.5-10.0	mmol/l
Haematocrit	0.25	0.34	0.34	0.35-0.45	l/l
MCV	69	77	77	80-100	Fl
Platelet count	467	273	318	150-400	10^9/l
Leucocytes	13.5	10.8	9.1	4.0-10.0	10^9/l
Electrolytes and renal parameters					
Sodium	142	149	140	135-145	mmol/l
Potassium	1.4	3.3	4.5	3.5-4.8	mmol/l
Chloride	81	110	104	97-107	mmol/l
Phosphate	1.4	0.8		0.8-1.5	mmol/l
Magnesium	0.68	0.70		0.7-1.1	mmol/l
Urea	3.2	5.3	8.0	2.9-7.5	mmol/l
Creatinine	126	83	81	40-90	µmol/l
Albumin	27.8	22.7	26.8	35-50	g/l
Arterial blood gas					
pH	7.53	7.44	7.41	7.35-7.45	
pCO2	8.9	6.0	7.3	4.3-6.0	kPa
pO2	11.5	11.6	10.9	11.0-14.4	kPa
HCO3-	56	30	34	22-29	mmol/l
Base excess	29.2	5.9	8.5	-3.0-3.0	mmol/l
Lactate	1.4			0.5-2.2	mmol/l
Hormonal parameters (serum)					
Renin	3.2	<3.0		mei-47	mU/l
Aldosterone	0.11	0.12		0.04-0.35	nmol/l
Glucose	8.2	7.4	6.3	4.0-7.8	mmol/l
ACTH		23		<46	ng/l
Cortisol	22:30h 0.73	08:00h 0.56 16:00h 0.68		0.15-0.70 0.10-0.45	µmol/l
Osmolality					
Osmolality		308		275-300	mOsmol/kg
Osmol gap		-3		< 10	mOsm/kg
Anion gap	6.4	16.6		13-17	mmol/l
				Corrected: 10.5-14.5 l*	

T0= Presentation at ED/admittance upon ICU; T1= Post extubation; T2= Day of discharge to department of internal medicine; ED=emergency department; ICU= intensive care unit

Anion gap calculated as ([Na+] + [K+] – ([HCO3-] + [Cl-]) + (0.25*(40-[Alb]))
Osmol gap calculated as serum osmolality - ((2 x [Na+]) + [glucose] + [urea])

* Correction of normal value for hypoalbuminaemia [13]

The metabolic disturbances suggested a problem in the renin-angiotensin-aldosterone system. Diagnostic considerations included primary hyperaldosteronism (e.g. an aldosterone producing tumour or adrenal hyperplasia), secondary hyperaldosteronism (e.g. renovascular disease), and non-aldosterone mineralocorticoid excess (e.g. liquorice abuse). After extubation, a thorough medical history revealed an exceptional eating pattern: almost no vegetables, meat or fruit intake, an abuse of soda drinks, peppermint and an extraordinary abuse of the candy 'Fisherman's Friend', combined with regular forced vomiting. At home she consumed approximately 20 bags of Fisherman's Friend (each 25 grams) a day, corresponding to a daily intake of 460 lozenges containing 3000 mg of glycyrrhizin, the main constituent of liquorice. Liquorice intake at these levels can lead to a syndrome similar to primary hyperaldosteronism, called pseudohyperaldosteronism.

After two weeks of treatment in the ICU, her severe hypertension and metabolic disturbances improved significantly as displayed in *figure 1*, and the patient could be discharged to the department of internal medicine. Hormone levels of plasma renin and aldosterone were measured and an additional CT scan showed no evidence of adrenal tumours.

The only initial clues for a correct diagnosis were masked by an atypical presentation with pulmonary sepsis which might have suppressed the severity of the hypertension. Nevertheless, the differential diagnosis of the classic triad, severe hypertension, hypokalaemia and metabolic alkalosis, could have led to the diagnosis of a possible liquorice intoxication and would be strengthened by the medical history. The first step to analyse hypokalaemia and hypertension is the assessment of specific hormone levels such as plasma renin and aldosterone. Unfortunately, specific hormone levels were not measured during her ICU admission due to a delay in diagnosis, but were measured afterwards in stored serum. On admission, this patient had low-normal levels of aldosterone and normal levels of ACTH, 0.11 nmol/l (N 0.04-0.35) and 23 ng/l (N < 46) respectively. Nevertheless, her cortisol level (22.30 h) was elevated and her renin level was slightly lowered, 0.73 µmol/l (N 0.10-0.45) and 3.2 mU/l (N 5-47), respectively. After extubation the patient maintained a low level of renin and low-normal level of aldosterone, <3.0 mU/l (N 5-47) and 0.12 nmol/l (N 0.04-0.35), respectively.

No further measurements of renin and aldosterone were taken due to the patient's significant clinical improvement. Contact with the patient's general practitioner revealed that she eventually made a full recovery.

Discussion

The presence of relative hypertension, hypokalaemia and metabolic alkalosis suggests a disturbance in the renin-angiotensin-aldosterone system. In this patient, this triad was masked by an atypical presentation of pulmonary sepsis. Nevertheless, a hypermineralocorticoid state could have been diagnosed earlier. Thorough medical history eventually led to the underlying explanation: extreme liquorice ingestion. The decreased consciousness of the patient on admission to the emergency department was probably caused by pulmonary sepsis. At that time it was impossible to perform a thorough medical history, but a more extensive heteroanamnesis might have revealed the excessive intake of liquorice several days earlier.

Liquorice is the root of the *Glycyrrhiza glabra* plant, which has been cultivated for human consumption by societies around the world for generations.[1] The natural sweetness of liquorice accounts for its popularity as a base for several products, as shown in *table 2*. It is derived from the bioactive component of the root: glycyrrhizin (glycyrrhizic acid).[1] Chronic liquorice ingestion can induce a syndrome with findings similar to those in primary hyperaldosteronism, called pseudohyperaldosteronism. The only unique feature of this syndrome is a non-increased plasma aldosterone concentration.

Table 2. Potential sources of glycyrrhizin

Potential sources	Examples
Candies	Fisherman's Friend
	Jelly beans
	Lollies (liquorice)
	Chewing gum
	Liquorice root
Liquorice tea	-
Chewing tobacco	-
Alcoholic drinks	Belgian beers
	Anisettes/Pernod/Ouzo
	Pastis brands
	Drop shot
Toothpaste	-
Cough mixtures	-

Liquorice mediates its effect on blood pressure via the action of glycyrrhizin on the kidney. Glycyrrhetinic acid, a major metabolite of glycyrrhizic acid, has slight mineralocorticoid activity. More importantly, this compound also impairs the action of the enzyme 11-beta-hydroxysteroid dehydrogenase that converts cortisol to cortisone in aldosterone target tissues such as the collecting tubules in the kidney. Cortisol binds with equal avidity as aldosterone to the mineralocorticoid receptor and circulates in a much higher concentration. Thus cortisol activates the mineralocorticoid receptor and produces a syndrome similar to primary hyperaldosteronism, called pseudohyperaldosteronism.[2,3] This mechanism is shown in *figure 2*.[4]

In hypotensive sepsis a complex neurohumoral response occurs to maintain blood pressure homeostasis, resulting in increased sympathetic responses and hypothalamic-pituitary-adrenal axis stimulation. The renin-angiotensin-aldosterone system is involved in preserving blood pressure homeostasis. Decreasing blood pressure and loss of blood volume will induce hormonal activation sequentially with renin, angiotensin I, angiotensin II and aldosterone. This results in elevated concentrations of cortisol, renin and aldosterone.[5] Nevertheless the patient in this case had hypertensive sepsis with a low level of renin and low-normal level of aldosterone, <3.0 mU/l (N 5-47) and 0.12 nmol/l (N 0.04-0.35) respectively.

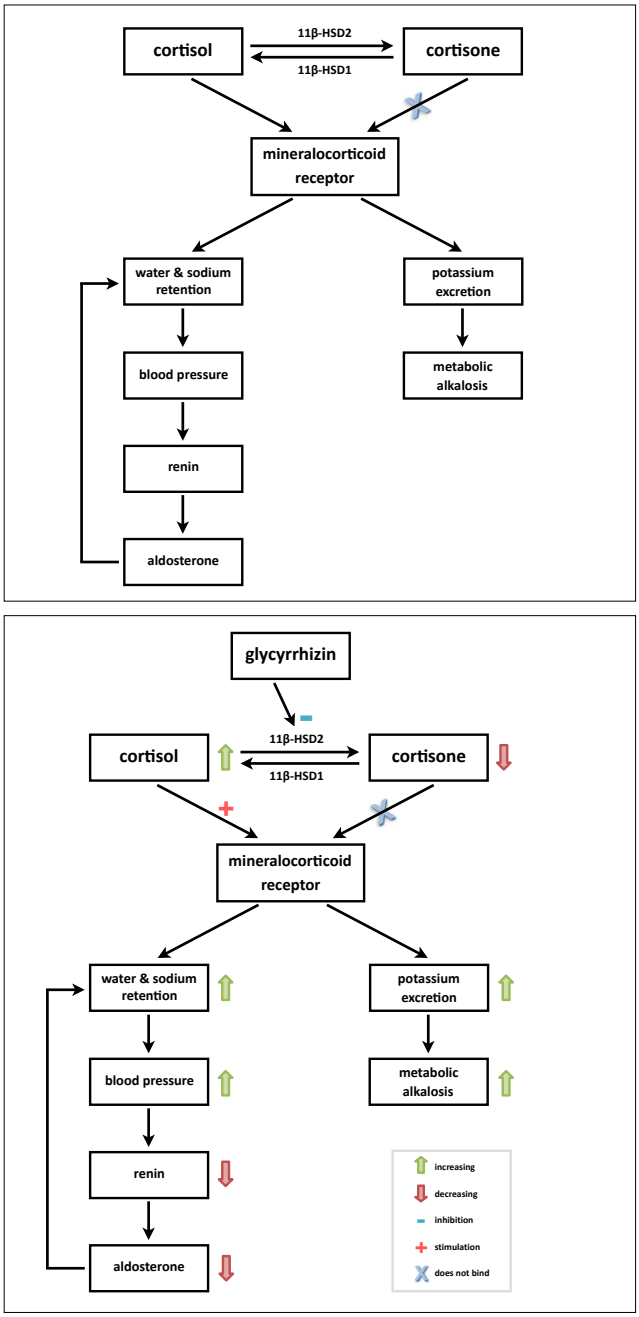

Figure 2. Effects of glycyrrhizin on the mineralocorticoid receptor
Adjusted from Foster et al.[4] In normal circumstances (a), cortisol is converted to inactive cortisone by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). In this situation, the normal function of the renin-angiotensin-aldosterone system (RAAS) maintains fluid and electrolyte balance with minimal effect of cortisol on the mineralocorticoid receptor.
Liquorice (b) contains glycyrrhizin which inhibits 11β-HSD2 activity, maintaining high cortisol concentration (much higher than aldosterone) so that cortisol now exerts much greater effect via binding to the mineralocorticoid receptor. This results in hypertension and hypokalaemia, both suppressing renin and aldosterone; and to a metabolic alkalosis provoked by the hypokalaemia.

One would expect an even more suppressed concentration of renin and aldosterone caused by negative feedback due to elevated blood pressure. The fact that aldosterone is not completely suppressed might suggest autonomous aldosterone production. This unexpected result might be explained by the pulmonary sepsis factor which in turn leads to hypovolaemia, generating a reverse effect on the renin and aldosterone concentration. The net effect would explain why the aldosterone concentration was only slightly decreased.

Pseudohyperaldosteronism is characterised by hypokalaemia, hypertension, metabolic alkalosis, and eventually a low plasma renin activity and plasma aldosterone level. The endogenous aldosterone secretion is appropriately suppressed in this setting. The extent of metabolic and acid-base derangement can occasionally be severe enough to cause serious complications.[6] In the kidney the intracellular acidosis induced by hypokalaemia promotes increased secretion of hydrogen ions, which can react with luminal bicarbonate, leading to bicarbonate retrieval or to urinary buffers such as ammonia to produce ammonium. This increase in hydrogen ion secretion increases net bicarbonate reabsorption and can contribute to high levels of bicarbonate and therefore metabolic alkalosis.[7]

Liquorice effects are seen within 3-10 days of the start of consumption and the maximal hypertensive effect occurs within two weeks.[8] The onset and severity of symptoms due to liquorice depend on the dose and duration of liquorice intake, as well as individual susceptibility.[9] The presence of partial 11b-hydroxysteroid dehydrogenase deficiency could explain why some people are susceptible to even low doses of glycyrrhizic acid. However, many other conditions could also cause acquired inhibition of the enzyme, such as chronic renal failure, hypothyroidism and some kinds of essential hypertension.[10] The extreme electrolyte disturbance in our patient could well have been the result of the older age, female sex and frequent vomiting, as these are known factors that increase the side effects of liquorice.[11]

Current regulations require liquorice products to be labelled with a warning that excessive consumption should be avoided in patients with hypertension. However, liquorice can also induce hypertension in normotensive subjects. Our patient had a daily intake of 3000 mg of liquorice. The European Scientific Committee on Food advises that regular glycyrrhizin doses of 100 mg/day present a risk to health and advocate a safe average daily intake of no more than 10 mg/person/day.[12] To our knowledge, such an exceptional intake of liquorice, 30 times the maximum advised daily intake, has not been described in literature before.

Stopping consumption of liquorice-containing products is the first step in acute management, in combination with potassium supplementation. The next step is to start mineralocorticoid receptor antagonists (e.g. spironolactone) or other potassium-sparing diuretics (e.g. amiloride).[4] Due to the risk of arrhythmias caused by the hypokalaemia, patients with a serum potassium level of less than 3.0 mmol/l should be referred to hospital for cardiac monitoring and potassium suppletion.[4] Despite the delay in the correct diagnosis, there was no delay in the correct initial treatment in the patient described here. Admission to the ICU inevitably resulted in the total withdrawal of the lozenges and the patient was immediately treated for her hypertension with spironolactone. The hypertensive effect may exist for some time despite withdrawal of liquorice, as observed in our case. Patients should be monitored after stopping liquorice intake until the blood pressure and potassium concentration reach normal levels. Literature suggests a period of up to four months before the renin suppression is overcome.[8]

Recommendations

Recognition of the triad (1) severe hypertension, (2) metabolic alkalosis and (3) hypokalaemia in the light of a pseudohyperaldosteronism is important to lead to a correct diagnosis. A thorough medical history can be crucial for the diagnosis, especially with an atypical presentation caused by a concomitant disease. Laboratory testing of renin and aldosterone blood levels can confirm the diagnosis of pseudohyperaldosteronism.

Key points

- Thorough medical history of diet (especially liquorice-containing products), dietary supplements and alternative medications is advisable in all cases of hypertension, even more so with concurrent hypokalaemia and metabolic alkalosis.
- The diagnosis of pseudohyperaldosteronism can be a challenge, especially when it is difficult to obtain a thorough medical history, for example when patients have a lower level of consciousness. Symptoms can be masked by other causes of haemodynamic/respiratory failure.
- Liquorice is a potent, reversible inducer of the mineralocorticoid effects of cortisol causing pseudohyperaldosteronism. Withdrawal of liquorice-containing products with support of mineralocorticoid receptor antagonists causes a slow but complete resolution of the symptoms of mineralocorticoid excess.

Disclosures

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