

Oedema induced by Glycyrrhiza glabra – case report **Obrzęk indukowany przez lukrecję gładką – opis przypadku**

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Summary

Background. Licorice (*Glycyrrhiza glabra*) containing about 400 different chemical components is a valuable herbal raw material used in the pharmaceutical and food industry. The compounds contained in it exhibit a wide and diverse spectrum of biological activity, e.g. antiulcer, antiviral, secretolytic, antiallergic, antibacterial, anti-inflammatory, antifungal. The use of this medicinal plant in various pharmaceutical forms can lead to adverse effects, including a set of symptoms called apparent mineralocorticoid excess or pseudohyperaldosteronism, including hypertension, peripheral oedema, hypokalemia and metabolic alkalosis. **Material and methods.** We present a case report of a 31-year-old woman using only oral contraception, in whom licorice supplementation caused swelling of the legs. **Results.** Two weeks after discontinuation of the supplement swelling subsided. **Conclusions.** The described case confirms the risk of an adverse effect associated with the mechanism of action of substances contained in licorice. Glycyrrhizin, the main active compound of Licorice is a known inhibitor of the type 2 isoenzyme of 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD2) and thus prevents cortisol inactivation. Elevated cortisol contributes to its increased affinity for mineralocorticoid receptors in the kidneys resulting in the reabsorption of sodium and water that leads to increases in intravascular volume and capillary hydrostatic pressures that contribute to oedema formation. (*Farm Współ 2020; 13: 113-118*)

Keywords: Glycyrrhiza glabra, oedema

Streszczenie

Wstęp. Lukrecja gładka (*Glycyrrhiza glabra*) zawierająca około 400 różnych składników chemicznych jest cennym surowcem zielarskim wykorzystywanym w przemyśle farmaceutycznym i spożywczym. Zawarte w niej związki wykazują szerokie i różnorodne spektrum działania biologicznego np. przeciwwrzdodowe, przeciwwirusowe, sekretolityczne, przeciwalergiczne, przeciwbakteryjne, przeciwzapalne, przeciwgrzybicze. Stosowanie tej rośliny leczniczej w różnych postaciach farmaceutycznych może prowadzić do wystąpienia działań niepożądanych, w tym zespołu objawów, zwanego pozornym nadmiarem mineralokortykoidów lub rzekomym hiperaldosteronizmem, obejmującego nadciśnienie tętnicze, obrzęki obwodowe, hipokaliemię oraz zasadowicę metaboliczną. **Material i metody.** Przedstawiamy przypadek 31-letniej kobiety stosującej jedynie doustną antykoncepcję, u której suplementacja lukrecji gładkiej spowodowała wystąpienie obrzęku nóg. **Wyniki.** Dwa tygodnie po zaprzestaniu stosowania suplementu obrzęki ustąpiły. **Wnioski.** Opisany przypadek potwierdza ryzyko wystąpienia działania niepożądanego związanego z mechanizmem działania substancji zawartych w lukrecji gładkiej. Glicyryzyna, główny składnik aktywny lukrecji, jest inhibitorem dehydrogenazy 11beta-hydroksysteroidowej typu 2 (11 beta-HSD2), a zatem zapobiega inaktywacji kortyzolu. Podwyższony poziom kortyzolu przyczynia się do zwiększenia jego powinowactwa względem receptorów mineralokortykoidów w nerkach, powodując reabsorpcję sodu i wody, co prowadzi do wzrostu objętości wewnątrznaczyniowej i kapilarnych ciśnień hydrostatycznych, które przyczyniają się do powstawania obrzęku. (*Farm Współ 2020; 13: 113-118*)

Słowa kluczowe: lukrecja gładka (Glycyrrhiza glabra), obrzęki

Introduction

From ancient times plants have been a major source of therapeutic agents in all cultures. Nowadays, herbal medicine is still considered highly effective and is a part of modern life style.

Glycyrrhiza glabra, also called licorice, liquorice, *glycyrrhiza* (from the Greek words glykos – sweet and rhiza – root), sweet wood. This herbaceous perennial belongs to the Fabaceae (Leguminosae) family and is native to Mediterranean areas, however is now also present in India, Russia, and China (the *Glycyrrhiza* genus contains more than 30 species distributed all over the world). Considering the phenotype, *G. glabra* can reach to 1 m in height, has pinnate leaves with a length of 7 to 15 cm, purple to whitish blue flowers arranged in a hermaphrodite inflorescence and oblong fruit with 2 to 3 cm of length, containing several seeds. Just like other representatives of Fabaceae, *G. glabra* can live in symbiosis with bacteria of the genus *Rhizobium* at the root level to fix nitrogen, which helps to accommodate to less fertile soils [1-2]. *G. glabra* is a popular herbal raw material used in the pharmaceutical and food industry but also in the manufacture of functional foods and food supplements. The therapeutic properties of this herb are well known since ancient times [3]. More than 20 triterpenoids and 300 flavonoids have been isolated from *G. glabra* [4]. The roots contain the vast amount of these constituents, but certain ones are also present (in smaller quantities) in leaves [2]. Therefore, the medicinal raw material is licorice root (*Glycyrrhizae radix*) with stolons, characterized by yellow color (due to the flavonoid content) and sweet taste (because of triterpene saponins presence). The main components of the raw material are above mentioned triterpene saponins, among them glycyrrhizin, as well as potassium, calcium and ammonium salts of glycyrrhizinic acid (2,0-15%) [5]. The primary active ingredient is glycyrrhizin. This triterpenoid saponin constitutes up to 25% of the licorice root extract (about 10% of the root dry weight) and is almost 50 times sweeter than sucrose. Glycyrrhizin is formed of two molecules of glucuronic acid and one molecule of glycyrrhetic acid. Chemical analysis revealed that raw form of licorice contents 47.11% of carbohydrate, 24.48% of fiber, 9.15% of protein, 3.56% of silica and 0.53% of fat [6]. The raw material also contains flavonoids, coumarin, bitter substances, resins, phytosterols, asparagine, lipids and traces of essential oil, lipid compounds, organic acids, betaine, choline, amino acids and mineral salts.

The compounds contained in licorice exhibit a broad spectrum of biological activity, such as antitumor, antimicrobial, antiviral, anti-inflammatory, immunoregulatory, secretolytic and antiallergic properties. It is also thought to be beneficial in the recovery and protection of the nervous, alimentary, respiratory, endocrine, and cardiovascular systems, therefore the roots have been used in the traditional medicine to treat chest and lung diseases (pneumonia, bronchitis, arthritis, bronchial asthma), coughs, skin diseases, allergies, swellings, fluid retention, low blood pressure, heart diseases, kidney diseases, gastric ulcer, liver toxicity, hyperglycemia, pancreatic disorders, Addison's disease and many others [4,7]. It is also used in the cosmetics industry due to soothing, moisturizing, whitening and protective effects on the skin [5]. Biological activity of this herb has made it a popular ingredient used in the pharmaceutical industry for the production of dietary supplements, tablets, teas and herbal mixtures. Considering its characteristic flavor, licorice has been used in the food industry as a sweetener and an additive to many types of spices (in the form of powdered root, dry extract, extract or ammonium salt of glycyrrhizinic acid). Apart from that, approximately 80% of industrially harvested licorice was used as an additive to tobacco in the 1980s [8]. As of today, we are struggling with the pandemic of SARS-CoV-2. As with many other diseases, people seek remedies and medicinal substances in nature. And so it is with the COVID-19. Due to the antiviral properties of licorice, it has become the object of interest [9]. Unfortunately, this is not just about scientists, but also unaware patients trying to heal on their own, without regard to the consequences of misuse and adverse effects.

Case report

A 31-year-old woman with leg swelling came to general practitioner. The interview indicated that she had been taking oral contraception for 3 years (desogestrel 75 µg/day). Chronic diseases and adverse reactions to occasional medications (painkillers, antibacterials) and oral contraceptives were excluded. Laboratory tests performed five months earlier (blood counts, fasting glucose, lipidogram, liver enzymes, electrolytes) and physical examination results gave correct results. The patient took a diet supplement containing standardized powdered licorice root extract 250 mg and powdered unprocessed licorice root 225 mg three times a day for 3 months as part of

antiviral prophylaxis. Before visiting the doctor, the patient used a combination preparation (nettle herb extract, green tea extract, grape seed extract, dandelion extract) advertised as a remedy containing natural ingredients supporting, among others, elimination of water from the body for a week. Blood pressure measurement taken during the visit gave correct result. Medical recommendation – discontinuation of the licorice dietary supplement. After a week of licorice supplementation withdrawal the swelling resolved.

Discussion

Despite the valuable medicinal properties of licorice, its intake may entail various negative consequences. Glycyrrhizin high and/or prolonged consumption can lead to a set of symptoms called apparent mineralocorticoid excess or pseudoaldosteronism, which include hypertension (with symptoms of encephalopathy), peripheral oedema, hypokalemia, metabolic alkalosis and suppression of renin aldosterone. Recent studies have given an insight into the mechanism of this toxic effect. Glycyrrhizinic acid, or rather its aglycone gly-

cyrrhetic acid (GE), is formed in the small intestine as a result of the hydrolytic breakdown by *Eubacterium sp.* bacteria [8] Glycyrrhetic acid is an inhibitor of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2). 11 β -HSD dehydrogenase is responsible for intra-systemic homeostasis of cortisol and cortisone, which is about 300 times less active. Two 11 β -HSD isoforms can be distinguished: type 1 and type 2. Both forms differ in organ expression and affinity for catalyzed substrates. Isoform 1 (11 β -HSD1), NADPH-dependent, with high affinity for cortisone and low for cortisol, occurs mainly in the liver and adipose tissue. *In vivo*, it mainly exhibits reductase activity, conditioning the correspondingly high concentration of active cortisol in tissues containing glucocorticosteroid receptors. Isoform 2 (11 β -HSD2), with high affinity for cortisol, is found mainly in kidneys, but also occurs in the large intestine, salivary glands, pancreas and gonads. It only exhibits NAD⁺-dependent dehydrogenase activity, oxidizing cortisol to cortisone, protecting tissues with mineralocorticoid receptors (MR) against cortisol. Cortisol, unlike cortisone, has the ability to activate MR

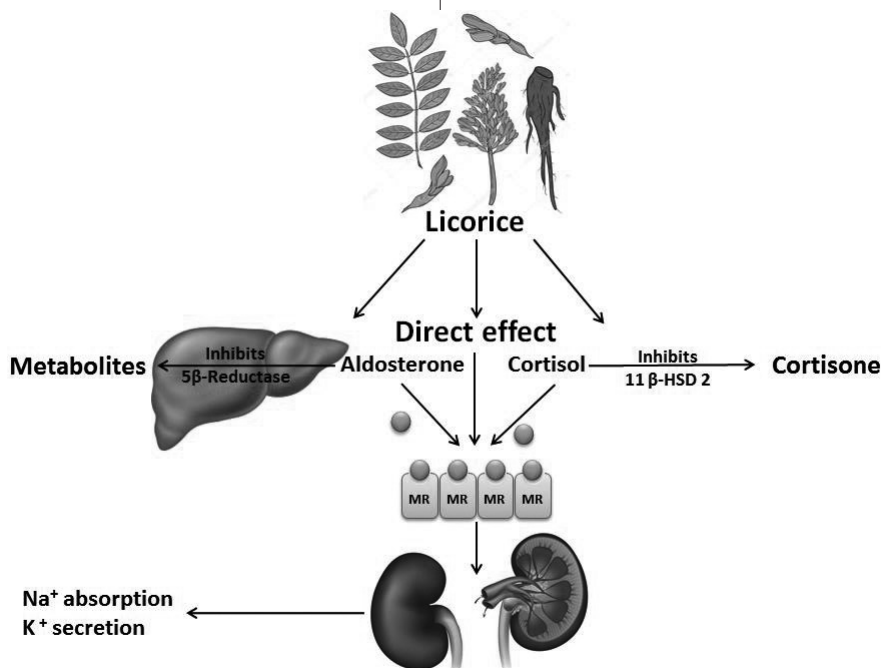


Figure 1. Licorice adverse reactions results from its action through various mechanisms: inhibition of 11- β -hydroxysteroid dehydrogenase type 2, 5 β -reductase (which metabolizes aldosterone) and its direct action on the mineralocorticoid receptors causing sodium reabsorption and potassium secretion. MR, mineralocorticoid receptor; 11- β -HSD 2, 11- β -hydroxysteroid dehydrogenase type 2 [10]

receptors similar to aldosterone, however, it is present in the body in 100-1000 times higher concentration than aldosterone. Blockade of the 11 β -HSD2 enzyme by glycyrrhetic acid or carbenoxolone results in activation of MR receptors by cortisol, bypassing the control by the renin-angiotensin-aldosterone (RAA) system leading to sodium reabsorption and potassium excretion with transient hypernatremia, persistent hypokalemia, hypertension, and metabolic alkalosis (Figure 1). Clinically significant inhibition of the 11 β -HSD2 enzyme in the kidneys leads to effects similar to those of primary hyperaldosteronism, however, this occurs when the RAA system is inhibited (low plasma renin activity, low aldosterone concentration). We are therefore dealing with an acquired condition of apparent mineralocorticosteroid excess [8,10].

In the literature, we can find many casuistic descriptions of swelling associated with licorice. Considerable individual variation in the susceptibility to glycyrrhizic acid can be noticed. Regarding the most susceptible individuals, to produce adverse effect only about 100 mg of glycyrrhizic acid (0.2% glycyrrhizic acid = about 50 g licorice sweets) in a regular daily intake seems to be sufficient [11]. 45-year-old male patient with complaints of oedema and weakness, had consumed about 1 L of licorice syrup a day (about 200 mg glycyrrhizic acid) for 4 days and 2.5 L of syrup (about 500 mg *glycyrrhizic acid*) on day 5. Due to excessive licorice intake this person developed water and sodium retention, oedema, hypokalemia and also decrease in platelets, but, what is interesting, there was no rise in his blood pressure. He was advised to stop drinking licorice syrup (no medication was recommended). After three days, physical examination showed that the findings returned to normal. Blood test was evaluated as normal, there was no sign of thrombocytopenia and hypokalemia. After a month of weekly clinical controls, oedema was not observed again. The patient had made a full recovery [11]. Another case concerns a 15-year-old healthy boy with report of hypertension encephalopathy after ingestion of 0.5 kg licorice candy. After about three hours he developed serious headache, nausea, vomiting, and right-sided weakness. Blood pressure measurements indicated 200-130 mmHg. The next morning the hemiparesis was increased and the patient was admitted to the hospital. He recovered completely in the course of 5 months [12].

Consumption of licorice flavoured chewing gums with glycyrrhizin content contributed to development

of hypokalaemia in two patients with hypertension or oedema. The first 21 year old woman patient, using an oral contraceptive, presented headache and hypertension as her blood pressure was 190/120 mmHg. She declared an intake of about 100 g of liquorice daily. Patient was advised to stop eating licorice and taking the oral contraceptive, but she still had her blood pressure raised even after treatment with a combination of atenolol, lisinopril, hydrochlorothiazide and amlodipine. Patient admitted to replacement of her licorice daily intake by chewing gum and whereby, her daily intake of glycyrrhizic acid was about 120 mg. She gave up chewing gum and after three weeks her blood pressure was 110/80 mmHg and plasma potassium concentration 5.3 mmol/L. The second case was a 35 year old woman with profound hypokalaemia of 2.2 mmol/l. The patient took chlorothiazide 500 mg twice a day because of pretibial oedema. She was also using an oral contraceptive. The result of clinical examination was pitting oedema, blood pressure was 140/80 mm, plasma potassium and bicarbonate concentrations were 2.2 mmol/L (intravenous and oral potassium supplementation was required) and 30.8 mmol/L, respectively. She frequently used liquorice flavoured chewing gum containing 160 mg licorice, of which 10% is glycyrrhizic acid, in each 16 g packet. She used about three packets a day (50 mg glycyrrhizic acid). Patient was advised to quit the gum. Three weeks after cessation of chewing gum, patient's oedema had disappeared completely, blood pressure had fallen to 110/80 mmHg, plasma potassium had risen to 4.2 mmol/l and also other electrolyte concentrations returned to normal state [13].

Apart from that, dizziness, arrhythmias, acute renal failure, weakness of the heart muscle and other muscles and cardiomyopathy may also appear. The daily amount of licorice ingested by patients with mineralocorticoid excess syndromes varies over a wide range 1.5-250 g per day. The recommended amount is 5 to 15 g licorice root per day, which corresponds to 200-600 mg of glycyrrhizin per day and no longer than 4-6 weeks without consulting a doctor [8,10]. Glycyrrhizin is poorly absorbed by the gastrointestinal tract but extensively metabolized by the intestinal microflora to 18-glycyrrhetic acid 3-omonoglucuronide and glycyrrhetic acid, which are readily absorbed. Then, the glycyrrhetic acid can enter enterohepatic circulation- this process usually requires several days to eliminate the acid completely. Products containing

licorice extract should not be consumed by patients suffering from liver diseases associated with cholestasis, cirrhosis, severe renal failure and also during pregnancy [2,8]. The use of licorice should be cautioned in pregnancy and neonates as *G. glabra* and glycyrrhizin salts possess weak mutagenicity, genotoxicity, carcinogenicity, and developmental toxicity effects. Other negative effects are reduction of gestational age, preterm delivery, and some change in hypothalamic-pituitary-adrenocortical axis function and cognitive dysfunction in delivered children [14].

Consumption of licorice-containing products when using pharmacotherapy is also associated with the risk of various types of drug interactions and also the severity or slight differences in the profile of side effects typical for this herb. Licorice taken together with thiazide and loop diuretics, sulfonamides or prednisolone additively increases the loss of potassium ions, which can lead to hypokalemia with its dangerous consequences. In the same mechanism, licorice increases the risk of digitalis glycoside toxicity. Taking licorice during warfarin therapy increases the effect of the latter, causing an increased risk of hemorrhagic complications. It should be mentioned that the licorice extract, by inhibiting the activity of various cytochrome P450 isoforms, slows down the metabolism of many drugs, which as a result may reveal the toxic effect of too high dose or intensify side effects [15]. Particularly noteworthy is to mention that licorice used together with oral contraceptives, that are known to increase sensitivity to glycyrrhizinic acid, exerts the effect of enhancing the above-mentioned symptoms [5].

Conclusion

There is a great scope in utilizing herbal medicine worldwide nowadays. However, despite multiple health-promoting properties, confirmed by various studies and many years of experience of people around the world, over the centuries, herbal drugs are composed of many known and unknown substances that may exert harmful effects on human health. The case report cited in the article suggests the need to pay attention to plant preparations and supplements used for various purposes. This applies not only to licorice, but also to many other herbs, that are used by people consciously or not, for various health problems, often without any knowledge of side effects or interactions. With regard to the possible individual sensitivity even to low doses of glycyrrhizin, the duration of ingestion and possible interactions with drugs and herbs, it is really difficult to precisely determine safe doses of licorice. Harmful complications such as hypokalemia, oedema, and thrombocytopenia and many others may be related to licorice usage. Therefore the practitioners should take detailed medicine intake histories into account and take all precautions before deciding to start licorice supplementation.

Conflict of interest

None

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