The cardiovascular complications of licorice

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Licorice is a US Food and Drug Administration approved food supplement present in various forms without strict policies to regulate its consumption and to prevent toxicity. It is widely utilized as a sweetener, a thirst quencher, in various candies and drinks, and has some medicinal applications. The health benefits of licorice are minor compared to the adverse outcomes of chronic use which is never justified nor recommended. The long-established belief among the community that licorice is a natural healthy substance free of side effects promotes its liberal consumption and predisposition to toxicity. This merits further nationwide education through different media types on the health hazards of chronic licorice intake and the tolerable upper limit of daily ingestion. The main mode of action is through inhibition of the enzyme 11-β-hydroxysteroid dehydrogenase, resulting in a mineralocorticoid effect. This aldosterone-like action is the basic principle for understanding its health benefits and the wide spectrum of adverse effects. Among the various complications associated with excess licorice intake, effects on the cardiovascular system are the most serious. Herein is a review of the various cardiovascular complications associated with licorice intake. I hope that this review will caution physicians, exposed patients, and manufacturing companies against the detrimental effects of licorice and impel the Food and Drug Administration to actively control the use of this substance. *Cardiovasc Endocrinol* 2:46–49 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Cardiovascular Endocrinology 2013, **2**:46–49

Keywords: arrhythmia, glycyrrhetic acid, glycyrrhizin, hyperaldosteronism, hypertension, licorice, liquorice, pseudohyperaldosteronism

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Received 15 October 2012 **Accepted** 6 April 2013

Licorice has a rich history, dating back since the ancient Egyptians and Assyrians BC. It is an extract of the plant *Glycyrrhiza*, whose name is derived from the Greek word 'glykos', meaning sweet, and 'rhiza', meaning root. Licorice is used in an enormous variety of products including licorice sticks, toffee bars, blackcurrant, Pontefract cakes, torpedos, stimorol chewing gums, erk-soos, Belgian beers, pastis brands, in addition to being a sweetener for tobacco products and certain medicinal preparations. In the USA, it is recognized as a safe flavoring agent and is accepted in many countries as a healthy natural substance. Nonetheless, evidence of favorable health benefits of licorice in human is limited. Many are unaware of its side effects and believe that it is a low-fat snack and a healthy food choice. The main mode of action is through its active metabolite, glycyrrhetic acid, which inhibits the enzyme 11-β-hydroxysteroid dehydrogenase (causing an increase in cortisol levels), with a resultant cortisol-induced mineralocorticoid effect through avid binding to mineralocorticoid receptors [1]. Other modes of action include the direct binding of licorice to mineralocorticoid receptors [2] and the inhibition of the hepatic metabolism of aldosterone through suppression of 5-β reductase activity [3]. It is now clear that the inhibition of 11-β-hydroxysteroid dehydrogenase is the main mode of action as the affinity of glycyrrhetic acid to the mineralocorticoid receptors is very weak. Pseudohyperaldosteronism is a state clinically mimicking hyperaldosteronism with suppression of plasma renin and aldosterone levels. Among the long list of causes (including dietary, genetic, and endocrinal factors), licorice is one of the important and unrecognized dietary triggers for pseudohyperaldosteronism. The tolerable upper limit of licorice ingestion has been provided by several societies. The European Union suggested that regular ingestion of glycyrrhizin should not exceed 100 mg/day (found in 60–70 g of licorice) [4]. The Dutch Nutrition Information Bureau advised against consumption of more than 200 mg of daily glycyrrhizin, assumed to correspond to 150 g of licorice confectionery [5]. Although it is suggested that sporadic or episodic licorice consumption does not carry the same risks as daily consumption, there are reports that demonstrate toxicity with episodic licorice intake. The lack of close regulation of the manufacture of licorice and the public unawareness of its health hazards promotes its toxicity.

The most common presentations of licorice toxicity are severe hypertension, hypokalemia, and myopathy, whereas the most serious is its cardiovascular complications. We have previously systematically reviewed the effects of licorice abuse on various body systems. Herein, I aim to focus on the cardiovascular complications of licorice. A systematic Pubmed search was performed to identify studies addressing the hazardous effects of licorice on the cardiovascular system. The keywords used included: licorice, liquorice, hyperaldosteronism, pseudo-hyperaldosteronism, glycyrrhizin, glycyrrhetic acid, arrhythmia, and hypertension. The references were then searched for

2162-688X © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/XCE.0b013e328362e3dd

Table 1 The cardiovascular complications arising from licorice consumption, taking into account the number of reported cases, presentations, and outcomes

Complication	*N*	Clinical presentation	Outcome
Cardiac arrhythmias [6–11]	7	Ventricular arrhythmias due to severe hypokalemia, causing prolongation of the QT interval	The majority of patients experienced a cardiac arrest with a subsequent recovery
Hypertension and hypokalemia [12–27]	23	Wide spectrum of presentation from mild to severe hypertension	Good prognosis. Patients responded well after cessation of licorice, starting antihypertensives and potassium supplementation. Longer time required occasionally for normalization of blood pressure
Hypertensive encephalopathy and stroke [28–30]	4	Three patients presented with hypertensive encephalopathy, one patient developed a stroke	Hypertensive encephalopathy was reversible with antihypertensives. All three patients recovered back to baseline. One patient with a focal neurological deficit recovered after 5 months [28]. One patient developed a stroke [30]
Congestive heart failure [31–33]	3	Profile of acute heart failure usually after a licorice binge in patients without previous cardiac disease	Improvement with antifailure measures
Generalized edema [34–36]	5	Generalized edema unrelated to heart failure	Good response to cessation of licorice and diuretics
Interaction with cardiac drugs [37–40]	1	Clinical symptoms due to inhibition of P450 and CYP3A4 systems, potentiating the effects of warfarin therapy. Digoxin toxicity occurred because of licorice-induced hypokalemia	In the patient with digoxin toxicity, the heart rate recovered 18 days after discontinuing licorice and digoxin

N, number of patients.

Fig. 1

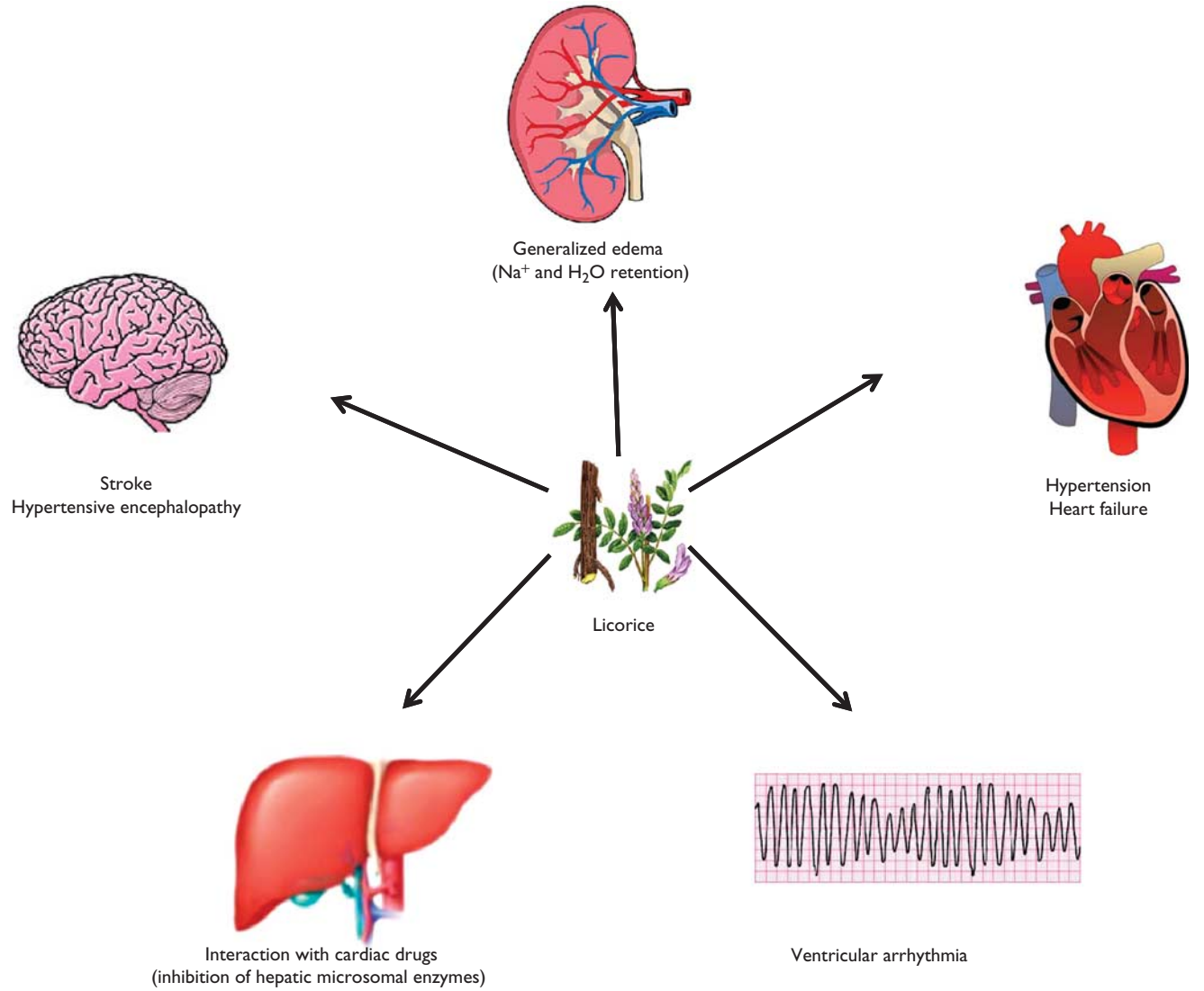

Illustration of the various cardiovascular complications arising from excess licorice intake.

the key terms. All studies in English language were included. Studies in other languages were included only if an English translation was provided. All articles up to the year 2010 were reviewed for the type of complication, number of affected individuals, and the final outcome. A total of 36 articles met the search criteria and were included in the review. Table 1 represents a compilation of the various cardiovascular complications arising from excess licorice intake.

The most serious cardiovascular complication arising from licorice intake relates to its arrhythmogenic potential. Chronic ingestion can lead to depletion of the body potassium stores. The extent of metabolic derangement can be severe enough to cause profound hypokalemia – a precursor of QT interval prolongation and ventricular arrhythmias. Cardiac arrest is a common associated feature, with a subsequent recovery in the majority of patients. Another complication frequently encountered after copious licorice intake is systemic hypertension. There is a wide continuum of presentations ranging from mild to severe resistant hypertension requiring hospitalization. Several patients developed hypertensive encephalopathy and one suffered a cerebrovascular accident [28–30]. The Na^+-retaining effect of licorice can lead to generalized edema [34–36] or more seriously acute heart failure and pulmonary edema [31–33], which usually occur after a licorice binge. Licorice-induced hypertension and hypervolemia is reversible once intake is stopped. Another group of complications relates to the interaction of licorice with cardiac medications. Some licorice root extracts can cause inhibition of the human liver microsomal cytochrome P450 and CYP3A4 systems [37,39]. The resultant decreased metabolism promotes toxicity with the use of certain cardiac drugs that require strict dosage adjustment such as warfarin. Digoxin toxicity from the hypokalemic effect of licorice has been previously reported [40]. Interestingly, Konik and colleagues described a case of licorice-incuced coronary artery spasm evident by the occurrence of chest pain, ST-segment elevation and normal coronary angiogram [41]. They attributed that to licorice-induced vasospasm via changes in endothelin and nitric oxide systems. This vasospastic effect of licorice was also demonstrated in a few cases of transient visual loss, migraines and posterior reversible encephalopathy syndrome. Figure 1 illustrates the various cardiovascular complications arising from excess licorice consumption.

An important step to diagnose licorice toxicity is to maintain a high index of suspicion and obtain a thorough dietary history with emphasis on licorice-containing products. Hypertension with hypokalemia, especially in a patient not receiving any diuretics provide an initial clue. Cessation of licorice intake should be immediately implemented in patients with toxicity. Aggressive potassium supplementation should be instituted in case of profound hypokalemia and arrhythmias. Cardiac monitoring is mandatory in patients with electrolyte derangements, especially in the presence of an underlying cardiac disease or arrhythmias. Serial electrocardiograms is crucial for monitoring patients with evidence of QTc interval prolongation on presentation. Aldosterone receptor antagonism with either spironolactone or eplerenone can be used as they counteract the action of licorice. Occasionally, more potent antihypertensives are required for resistant cases and for hypertensive emergencies. It is important to keep in mind that a substantial period of time is required to reverse licorice's mineralocorticoid-like effects due to its long half-life and the duration required for the renin–angiotensin–aldosterone axis to normalize, which can take up to 6 months [42].

In conclusion, patients with history of cardiac disease should be strongly cautioned from excess licorice intake. Those who are more susceptible to arrhythmias should minimize their licorice intake especially if they are concomitantly on medicines that lower potassium level (thiazide or loop diuretics). Patients with congestive heart failure or resistant hypertension should avoid licorice-containing products because of its salt-retaining effect. It is also advisable to avoid licorice intake in patients taking digoxin or warfarin because of the risk of toxicity. These recommendations should be more emphasized in countries that are known to be higher consumers of licorice.

Finally, the liberal consumption of licorice can never be justified, because its benefits are minor compared with the complications arising from chronic consumption [43]. Internists and endocrinologists are more familiar with this substance and its complications compared with cardiologists who are more likely to encounter these cases. I hope that this brief overview of the cardiovascular complications arising from the use of licorice will caution physicians, exposed patients, and manufacturing companies against the detrimental effects of licorice and impel the Food and Drug Administration to actively control the use of this substance.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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