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EDITORIAL

Liquorice and hypertension

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ABSTRACT

Glycyrrhetinic acid, the active constituent of liquorice, inhibits renal 11β-hydroxysteroid dehydrogenase. This allows cortisol to stimulate mineralocorticoid receptors, which can result in hypertension and hypokalaemia. Treatment options are based on pathophysiological understanding.

Liquorice, the root of the *Glycyrrhiza glabra*, has been used throughout the millennia for its taste and for medical purposes. Natural liquorice root was found in the 3000-year-old Tomb of King Tut. Soldiers of Alexander the Great's army chewed the root as a thirst quencher. Early Greek physicians as Hippocrates used natural liquorice to heal wounds and sore throats, and liquorice is an extremely important herb in Chinese medicine. In the Middle Ages it was used for treatment of hypotension. In 1946, the Dutch physician F.E. Revers demonstrated that liquorice was the active ingredient in a domestic medicine used in the Netherlands, and reported good results in the treatment of stomach ulcers. He also observed, however, that many patients developed hypokalaemia and an increase in blood pressure. Following this Borst *et al.* demonstrated that liquorice and cortisone had a synergistic effect in Addison's disease.[1] Later investigations showed that aldosterone secretion was suppressed in liquorice-induced hypertension, thus the expression 'pseudohyperaldosteronism' was used. The hypertension responds to spironolactone, a blocker of mineralocorticoid receptors (MRs), but no steroids stimulating the MRs could be identified.

The mechanism by which both liquorice and the apparent mineralocorticoid excess (AME) syndrome cause hypertension was not understood until the discovery of the 11β-hydroxysteroid dehydrogenase isozymes (11β-HSDs).[2] These isozymes catalyse the interconversion of cortisol and cortisone. 11β-HSD type 1 is most abundantly expressed in liver and adipose tissue, where it mainly functions as a reductase, converting inactive cortisone to active cortisol.[3,4]

The second isozyme, 11β-HSD2, is highly expressed in mineralocorticoid target tissues such as renal cortex[5,6] and salivary glands.[7] This isozyme has mainly dehydrogenase activity and is already active at very low cortisol concentrations. 11β-HSD2 plays a key role in regulating mineralocorticoid activity of cortisol. *In vivo* MRs are protected from exposure to cortisol by activity of 11β-HSD2. This isozyme rapidly metabolises the active mineralocorticoid cortisol to its inactive metabolite cortisone, thus preventing stimulation of MRs by cortisol. Aldosterone is not metabolised by 11β-HSD2 and can therefore bind to the MRs. Liquorice contains glycyrrhizin, in the intestine this is converted to glycyrrhetinic acid (GA) which is absorbed. GA inhibits activity of 11β-HSD2, this allows cortisol to bind to the MRs resulting in a hypermineralocorticoid state. Two case reports in this issue of the Netherlands Journal of Medicine demonstrate that liquorice-induced effects can present in very different ways. The report by Van den Bosch *et al.* reminds us that chronic liquorice intake can result in very serious symptoms, including rhabdomyolysis and paralyis.[8] The case report by Janse *et al.* demonstrates that liquorice-induced hypertension can occur at any age, and that a high level of suspicion is required to elucidate liquorice abuse.[9] This is also illustrated by the story of a 42-year-old female patient in Ontario, Canada. She developed hypokalaemia and mild hypertension without apparent cause. Only after several weeks it became clear that her family in the Netherlands had sent her boxes of liquorice as a Christmas present. As she enjoyed the taste she finished the boxes within a few weeks, resulting in the clinical situation described. It should be noted that GA can also be ingested from a variety of other products, including laxatives,[10] liquorice tea,[11] and Chinese medicines.[12]

When liquorice is suspected to be the cause of hypokalaemia and/or hypertension, the diagnosis can be confirmed by measuring plasma levels of GA,[13] or by demonstrating an increased ratio of cortisol over cortisone in plasma, saliva or urine.[14] In clinical practice, discontinuation of liquorice intake will often be sufficient.

How much liquorice is required to develop symptoms? This will depend on the amount of GA in the liquorice, as there is a clear dose-response relation between GA

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and cortisol-cortisone ratio.[15] On average, 1 g of liquorice contains about 2 mg GA, but the amount of GA varies considerably, from 0.026 to 98 mg per gram liquorice.[16] The effect on blood pressure is also dose related: in a study in healthy volunteers, the increase in systolic blood pressure was 3 mmHg following 75 mg GA, and 14 mmHg following 540 mg GA a day.[17]

The sensitivity for the effect of liquorice varies between individuals. A daily dose of 100 g liquorice, containing 150 mg GA, resulted in an increase in systolic blood pressure of 15 mmHg in subjects with primary hypertension, while the increase was only 3.5 mmHg in normotensive subjects.[18] However, there was no difference in the urinary cortisol-cortisone ratio between the groups, suggesting that there was no difference in the inhibition of renal 11β-HSD2 activity by liquorice. It is not clear, therefore, whether patients with hypertension are more sensitive to the effect of liquorice on 11β-HSD2 activity, or that the difference is located at or post mineralocorticoid receptor level. Alternatively the effects could be located outside the kidneys. Some studies have suggested that there is a relation between 11β-HSD2 activity and salt sensitivity,[19] but other studies could not confirm this.[20] Case reports have shown that liquorice intake as low as 50 g a day has occasionally resulted in clinical effects.[21] One wonders if these patients had mutations in the 11β-HSD2 gene resulting in congenitally reduced activity of 11β-HSD2, rendering them more susceptible to the inhibitory effects of liquorice.

The treatment of patients with liquorice-induced hypertension and hypokalaemia is based on understanding the pathophysiology. The first step is recognition of liquorice as a cause, and discontinuation of its intake. Next steps may be administration of potassium and blockade of the MRs. In severe hypokalaemia, administration of dexamethasone could be considered, as this will suppress the endogenous production of cortisol, thus decreasing stimulation of MRs by cortisol.

In conclusion, the story of liquorice and its effect on blood pressure and potassium remains fascinating. It has been a very useful tool in the discovery of the importance of intracellular shuttling of cortisol and cortisone. Liquorice-induced effects can be encountered in patients of all ages and all over the world. In clinical practice, a high level of suspicion remains warranted in patients with unexplained hypokalaemia and/or hypertension.

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