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Question: What is the mechanism by which licorice (*Glycyrrhiza glabra*) causes swelling or edema?

Answer: Licorice (*Glycyrrhiza glabra*) contains an ingredient called glycyrrhizin or glycyrrhizic acid and has been used in the treatment of stomach ulcers, bronchitis, sore throat and even viral hepatitis.[1] It is available in a number of dosage forms that include powdered forms, capsules, tablets and liquid extracts.[1] Unfortunately, licorice ingestion can lead to excess mineralocorticoid activity that is manifested by suppressed renin levels, sodium retention, hypokalemia, hypertension and edema.[1-5] As it relates to edema, it can be caused one or more of the following: things known to influence vasculature oncotic pressures, vasomotor tone of the veins, permeability of the capillary membranes, lymphatic flow and/or intravascular volume. Of these various biologic mechanisms, the change in intravascular volume appears to be the major contributor to the increased risk in patients developing swelling or edema when taking licorice supplements.

What is the mechanism by which the Glycyrrhiza glabra in licorice can increase the intravascular volume?
The normal physiology for sodium-water retention is largely influenced by the expression of mineralocorticoids. While aldosterone is regarded as the main hormone binding to mineralocorticoid receptors involved in the regulation of sodium reabsorption and potassium excretion in the distal renal tubules of the kidney, cortisol also binds to this receptor with the same binding affinity as aldosterone. Interestingly, even though cortisol blood concentrations tend to be greater than aldosterone concentrations, the effect of aldosterone dominates in terms of regulating sodium and water reabsorption and blood volume.

If cortisol concentrations are greater than aldosterone and both have equal affinity for the mineralocorticoid receptor, why doesn't cortisol have a greater influence on the body's overall mineralocorticoid activity?
The type 2 isoenzyme of 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD2) is normally involved in regulating corticosteroid specificity in the gastrointestinal tract, kidney and salivary glands (see figure 1).[6] Cortisol (not aldosterone) is metabolized by 11 beta-HSD2 to cortisone, which does not bind to either the mineralocorticoid or glucocorticoid receptor. Without this inactivation of cortisol, there would be mineralocorticoid excess. In fact, there is an inherited disease called *syndrome of apparent mineralocorticoid excess* in which the mineralocorticoid receptor is overly activated thereby causing hypokalemia and hypervolemia due to the excessive reabsorption of sodium and water at the expense of potassium excretion. This is the same effect created by licorice use.

Licorice is a known inhibitor of 11 beta-HSD2 and thus prevents the inactivation of cortisol, thereby causing a state of excess mineralocorticoid activity or pseudohyperaldosteronism.[2-6] The increase in mineralocorticoid activity results in greater sodium and water reabsorption at the expense of potassium excretion. This will eventually manifest as an increase in hydrostatic and overall blood pressures thereby resulting in the development of edema.

The Details for Those Interested:

How does cortisol binding to the mineralocorticoid receptor in the distal renal tubule increase sodium and water reabsorption at the expense of potassium excretion?

The increased cortisol resulting from licorice use increases gene expression and availability of several enzymes. The first of these is the Na^+ ion permease enzyme, which allows for a greater number of sodium ions to cross from the lumen to the inside of the renal tubular cell. Next is Na^+/K^+ ATPase on the basal-lateral side of the renal tubular cell which acts to transfer the increased cytosolic Na^+ into the peritubular fluid resulting in a lowering of the intracellular electronegativity. Lastly, there is an increase in citrate synthase activity within the mitochondria for the purpose of increasing the number of ATP available to fuel the increase in Na^+/K^+ ATPase activity on the basal-lateral side of the renal tubular cell.[7-9]

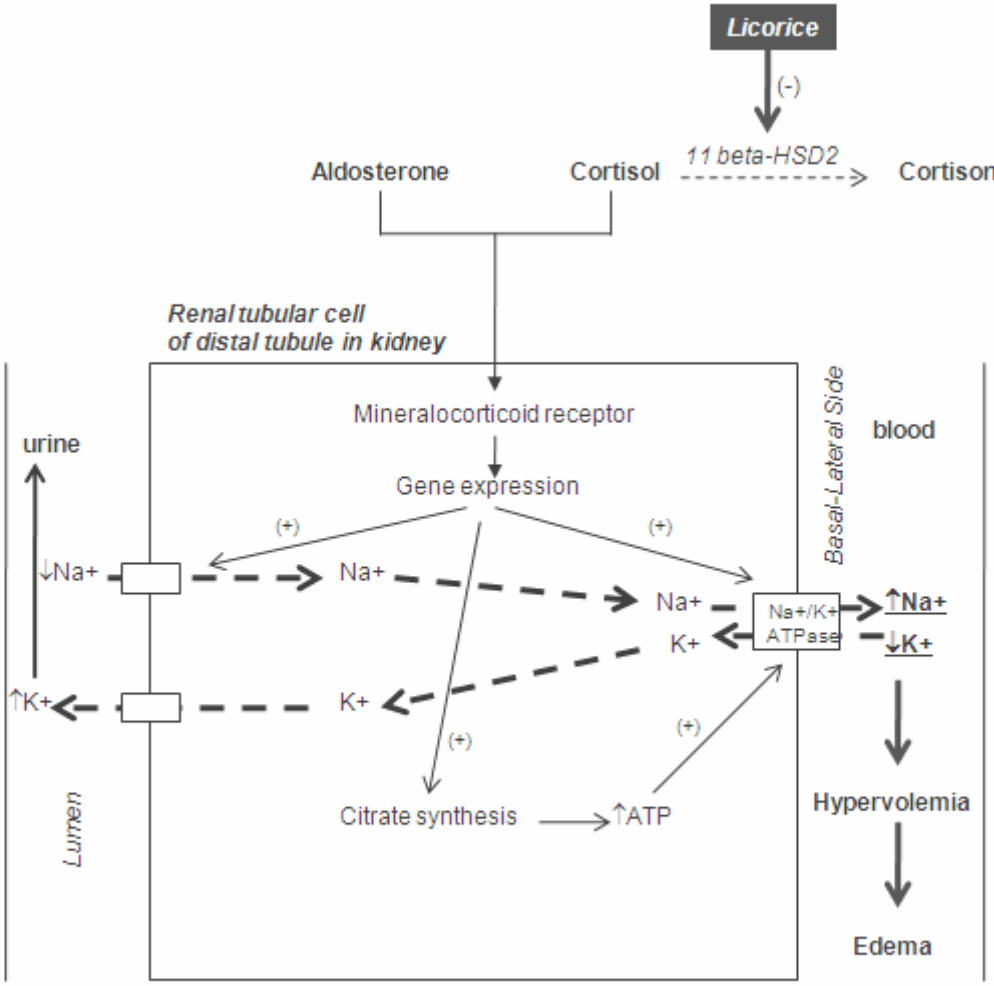

Figure 1. Mechanism of action for licorice-induced swelling or edema.

Conclusion

Excess mineralocorticoid activity and resulting increases in blood volume are clearly the main mechanisms by which licorice causes both edema and hypertension. In fact, the increase in blood pressure and development of hypertension can be significant and last several weeks before returning to baseline despite the discontinuation of the licorice supplementation.[2,4] Given the documented increases in edema and blood pressure, the use of licorice supplements should be taken into consideration for any patient with an unexplained increase in blood pressure, worsening of hypertension that is being adequately treated with antihypertensive medications and/or worsening of previously controlled heart failure. There is some evidence that spironolactone (Aldactone®) may confer some benefit on blood pressure; however, stopping the licorice would be the preferred recommendation for patients.[10]

(PW Nat Med Newsl 2009;1(41):1-4.)

Take Home Points:

- Licorice (*Glycyrrhiza glabra*) contains an ingredient called glycyrrhizin, also called glycyrrhizic acid, and has been used in the treatment of stomach ulcers, bronchitis, sore throat and even viral hepatitis.
- Unfortunately, licorice ingestion can lead to excess mineralocorticoid activity that is manifested by suppressed renin levels, sodium retention, hypervolemia, hypokalemia, hypertension and edema.
- Licorice is a known inhibitor of the type 2 isoenzyme of 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD2) and thus prevents to the inactivation of cortisol.
- The increased cortisol is available to bind to the mineralocorticoid receptor in the kidney resulting in the reabsorption of sodium and water that leads to increases in intravascular volume and capillary hydrostatic pressures that contribute to edema formation.

Considerations for Clinicians Based on Setting:

Outpatient Setting:
It may be worth evaluating for the use of licorice in any patient with unusual or unexplained edema, since licorice can be purchased over-the-counter (OTC) and on the internet by patients without your knowledge. This may be even more relevant if a patient is already on medications known to cause edema such as steroids and calcium channel blockers. Lastly, since licorice can increase the intravascular blood volume, it can also worsen blood pressure and may reduce the efficacy of other antihypertensives being used.

Inpatient Setting:
While licorice use is not likely to occur in the hospital, clinicians should include its use by the patient in the differential diagnosis when patients present with unexplained swelling and edema also in the presence of increased blood pressure/hypertension. Furthermore, this could be especially important in a patient with otherwise stable heart failure but is experiencing an exacerbation despite compliance with other medications, fluid intake and diet.

Important Counseling Bullet Point(s):

- As it relates to patients with underlying cardiovascular disease and/or uncontrolled hypertension, it would be important for clinicians to counsel their patients to avoid taking any OTC and/or natural medicines/supplements without consulting with you or their primary care physician since supplements like licorice are known to increase blood volume and/or blood pressure.

Medical/Legal Consideration(s):

- There were no cases identified in the 2008 edition of LexisNexis' Drugs in Litigation regarding licorice, and Pharmacology Weekly's legal counsel has not identified any such cases to date.[11] Nevertheless, because of the risk which has now been clearly identified in the medical field, medical professionals should counsel their patients to avoid taking licorice or any natural medicines without consulting their physician, and it would be prudent to document in the medical chart that the patient has been advised of the effect of licorice on blood pressure.

Test Questions for CE:

What is the common name for Glycyrrhiza glabra?
a. Licorice
b. Saw Palmetto
c. Cat's Claw
d. Bog Bean

Which of the following is a potential side effect with the use of Glycyrrhiza glabra?
a. Bronchoconstriction
b. Aplastic anemia
c. Hypotension
d. Edema

What other common prescription medication used along with Glycyrrhiza glabra can contribute to its effect on intravascular volume?

a. Steroids (such as prednisone)
b. Mirtazapine
c. Tiotropium
d. Bisacodyl

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