Glycyrrhizic acid toxicity caused by consumption of licorice candy cigars

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ABSTRACT

A 49-year-old female physician presented with peripheral edema, weight gain and relative hypertension caused by the consumption of licorice candy cigars containing glycyrrhizic acid (GZA) found in natural licorice extract. Although the patient's response to GZA resolved spontaneously, emergency physician awareness of the toxic effects of natural licorice extract may avert symptom progression in early-identified cases. The benefits of natural licorice extract as a flavour enhancer and herbal medicine are recognized worldwide. The Canadian public is likely not generally aware of the toxic potential of GZA, or that it may be present in the following commonly consumed products: black licorice, chewing gum, herbal teas, soft drinks, tobaccos and herbal remedies for cough, stomach ailments and constipation. Emergency physicians should inquire about the consumption of products that may contain natural licorice extract when patients present with unexplained hypertension, hypokalemia, edema, rhabdomyolysis or myoglobinuria.

Keywords: licorice, glycyrrhizic acid toxicity, hypermineralocorticoid syndrome

RÉSUMÉ

Une femme médecin de 49 ans présentait un œdème périphérique, un gain de poids et une hypertension relative causée par la consommation de cigares en réglisse contenant de l'acide glycyrrhizique que l'on retrouve dans l'extrait de réglisse naturelle. Bien que la réaction du patient à l'acide glycyrrhizique se soit résorbée spontanément, la sensibilisation des médecins d'urgence aux effets toxiques de l'extrait de réglisse naturelle pourrait permettre d'éviter la progression des symptômes pour les cas identifiés précocément. Les propriétés de l'extrait de réglisse naturelle comme rehausseur de goût et ses bienfaits comme médicament naturel sont connus dans le monde entier. Il y a de fortes chances que les Canadiens ne sont pas au courant de la toxicité potentielle de l'acide glycyrrhizique ou de sa présence dans les produits de consommation courants suivants : la réglisse noire, la gomme à mâcher, les tisanes, les boissons non alcoolisées, les produits du tabac ainsi que les plantes médicinales contre la toux, les maux d'estomac et la constipation. Les médecins d'urgence devraient poser des questions sur la consommation de produits qui pourraient contenir un extrait de réglisse naturelle lorsque des patients présentent des symptômes comme l'hypertension, l'hypokaliémie, des œdèmes ou la rhabdomyolyse ou la myoglobinurie.

Introduction

This report describes a case in which peripheral edema and weight gain were brought about by the daily consumption of licorice candy cigars over a 2-week period. Although the therapeutic and toxic effects of glycyrrhizic acid (GZA) have long been recognized worldwide, most licorice candy presently consumed in North America contains artificial

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flavouring rather than GZA. The general public is unlikely to be aware of the toxic potential of candy containing natural licorice. Emergency physicians should be aware of the variation in products labelled as licorice and the potential of natural licorice to cause significant toxicity.

Case report

A previously healthy 49-year-old female physician taking no medications presented to the emergency department (ED) with a 5-day history of markedly swollen legs. The patient noted some asymmetry, with the right leg being worse than the left. She complained of a feeling of tightness in her medial right thigh and requested a D-dimer assay to screen for deep vein thrombosis (DVT). The only risk factor for DVT was that over the previous 14 days the patient had twice sat in a car for 10-hour drives. She had taken no over-the-counter medications within 4 months of the ED visit.

While visiting family over the 2 weeks before presentation, the patient had gained 4.5 kg despite daily vigorous physical activity and her usual caloric intake. Her feet, ankles and thighs had swollen visibly, causing the loss of definition of the malleoli of both ankles. The patient reported aching and weakness in the muscles of both legs. When she returned from her vacation she had resumed her daily routine of inline skating and experienced no dsypnea or fatigue.

There were no genitourinary symptoms and the patient had been menopausal for 1 year. While on vacation, she noted 5 to 6 bowel movements per day, but because the facilities were limited to an outhouse, she was unable to describe stool consistency. The patient had a life-long history of travel-associated constipation and was aware of the laxative properties of licorice. Since licorice was one of her family's favourite candies, she had specifically brought a large quantity of licorice candy cigars to take on her vacation and had purposely consumed at least 4 per day, and as many as 7 on some days. She attributed the increase in her stool frequency to the licorice and considered this a therapeutic effect. No other family member had consumed more than 1 cigar per day and none reported a change in bowel habit, edema or weight gain.

On physical examination the patient appeared well apart from marked bilateral leg edema. Her blood pressure (BP) was 128/59 mm Hg, which was higher than her usual BP of 90–110 mm Hg systolic (last documented < 1 mo before presentation). Her heart rate was 78 beats/min and regular. Her weight was 63.6 kg.

The patient's D-dimer level was within the normal range and hemoglobin was 129 g/L. Serum sodium was 139 mmol/L, potassium 3.8 mmol/L, urea 2.4 mmol/L, creatinine 72 μmol/L and albumin 36 g/L. All liver function tests and a creatine kinase assay were within the normal ranges.

The patient was reassured that DVT was not the cause of her edema and sudden weight gain. She discharged herself from the ED to follow up with her family doctor. The patient resumed her normal activity, and, 2 days after her ED visit, a home scale revealed a weight of 62.3 kg. By 4 days after the ED visit her weight on the same home scale was 58.8 kg, which was her baseline weight. The peripheral edema and muscle aching had resolved completely. Her BP was 90/60 mm Hg and her heart rate was 74 beats/min. She had not ingested any licorice since 48 hours before her ED visit.

The diagnosis of GZA toxicity was made in hindsight, once it was recognized that the rapid fluctuation in peripheral edema, BP and weight corresponded to the commencement and subsequent cessation of natural licorice ingestion. Resolution of the edema and the return to baseline weight and BP were achieved 7 days after the consumption of licorice ceased. On follow-up at 7 months, the patient had no return of edema and no additional health concerns. Her weight remained at 58.5 kg and her BP was 94/60 mm Hg. She had consumed no black licorice during the 7 months after presentation.

Discussion

Emergency physicians should inquire about licorice consumption when obtaining a history from patients with unexplained hypertension, peripheral edema or hypokalemia. Although this patient's response to GZA resolved spontaneously, early emergency physician recognition of this widely available dietary indulgence may prevent the progression of toxicity in early-identified cases. Public awareness of either the pharmacologic effects of this candy or the difference between artificially flavoured licorice and black licorice containing extracts from the root of the plant *Glycyrrhiza glabra* is undoubtedly low. Other colours of licorice candy do not usually contain GZA.

Previous reports suggest that toxicity from licorice candy consumption can be dramatic.[1–5] ED presentation of hypokalemic paralysis has been described, as has intractable hypertension and rhabdomyolysis. Patients already on diuretics may be at particular risk for the toxic effects of GZA.[1,6] GZA toxicity typically progresses to fatigue, muscle weakness and hypokalemia and its manifestations, which include cardiac arrhythmias, fluid retention, rhabdomyolysis and myoglobinuria. However, reports of serious toxicity due to GZA are rare.

The pharmacology and physiologic effects of GZA are well understood.[7–10] GZA has both glucocorticoid and mineralocorticoid properties and can lead to a hypermineralocorticoid syndrome, and even present as pseudoprimary hyperaldosteronism. Although black licorice candy is the best known cause of GZA toxicity, other products commonly consumed in Canada may also contain GZA. These include some herbal teas, root beer, chewing gum and smoking and chewing tobaccos. GZA is commonly found in herbal remedies for cough, stomach ailments and constipation.[10] It is also reputed to be of benefit for adrenal insufficiency and liver cancer,[9] and to exhibit antibacterial and antiviral properties.[11] Most research on administering GZA to healthy volunteers has been done in Holland and Scandinavia.[12] Dutch licorice candy is assumed to contain 0.2% of GZA and one Dutch study recommends 6 g of licorice per day as a safe level of consumption.[13]

The licorice candy cigars consumed by this patient each weigh 19 g and contain 0.45 g of GZA according to information obtained directly from the Ontario manufacturer (Maria Miller, consumer representative, The Hershey Company: personal communication, 2007). Based on this, the patient consumed an estimated 1.8–3.2 g of GZA per day, which is significantly below the amount generally believed to cause symptoms.[13–15] Of note, potassium sorbate is an ingredient in the involved candy, and may have contributed to the patient being normokalemic. Additional ingredients of these licorice candy cigars include wheat flour, cooking molasses, liquid sugar, corn starch, salt, mineral oil, soy lecithin, natural flavour, dextrin, artificial colour and potassium sorbate.

Conclusion

Natural licorice, which originates from the root of the plant *Glycyrrhiza glabra*, is used worldwide in candies and other commonly consumed products.[16] The general public is unlikely to be aware of the potential for GZA toxicity. Emergency physicians should inquire about natural licorice extract consumption when patients present with unexplained hypertension, hypokalemia, edema, rhabdomyolsis or myoglobinuria.

Competing interests: None declared.

References

1. Achar KN, Abduo TJ, Menon NK, et al. Severe hypokalemic rhabdomyolysis due to ingestion of liquorice during Ramadan. Aust N Z J Med 1989;19:365-7.
2. Cuspidi C, Gelosa M, Moroni E, et al. Pseudo-Conn's syndrome after habitual ingestion of liquorice. Report on various clinical cases [article in Italian]. Minerva Med 1981;72:825-30.
3. Lorenzin F, Degen C, Milani A, et al. Pseudo-hyperaldosteronism caused by licorice. Pathogenetic considerations and presentation of a clinical case. Clin Ter 1990;132:55-8.
4. Lin SH, Yang SS, Chau T, et al. An unusual case of hypokalemic paralysis: chronic licorice ingestion. Am J Med Sci 2003;325:153-6.
5. Elinav E, Chajek-Shaul T. Licorice consumption causing severe hypokalemic paralysis. Mayo Clin Proc 2003;78:767-8.
6. van Uum SH. Liquorice and hypertension. Neth J Med 2005;63: 119-20.
7. Farese RV Jr, Biglieri EJ, Shackleton CHL, et al. Licorice-induced hypermineralocorticoidism. N Engl J Med 1991;325: 1223-7.
8. Subhuti D. Safety issues affecting herbs: herbs that may increase blood pressure. Portland (OR): Institute for Traditional Medicine; 2003. Available: www.itmonline.org/arts/hypertension.htm (accessed 2008 Sept 19).
9. Natural Standard Research Collaboration. Licorice *(Glycyrrhiza glabra L.)* and DGL (deglycyrrhizinated licorice). Cambridge (MA): The Collaboration; 2008. Available: www.nlm.nih.gov /medlineplus/druginfo/natural/patient-licorice.html (accessed 2008 Sept 19).
10. Schonwald S. Plant poisoning, licorice [article]. eMedicine 2008;Feb 13. Available: www.emedicine.com/emerg/topic 450.htm (accessed 2008 Sept 19).
11. Cinatl J, Morgenstern B, Bauer G, et al. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 2003;361:2045-6.
12. Sigurjónsdóttir HA, Franzson L, Manhem K, et al. Liquorice-induced rise in blood pressure: a linear dose-response relationship. J Hum Hypertens 2001;15:549-52.
13. van Gelderen CE, Bijlsma JA, van Dokkum W, et al. Glycyrrhizic acid: the assessment of a no effect level. Hum Exp Toxicol 2000;19:434-9.
14. De Klerk GJ, Nieuwenhuis MG, Beutler JJ, et al. Hypokalemia and hypertension associated with use of liquorice flavoured chewing gum. BMJ 1997;314:731-2.
15. Armanini D, Bonanni G, Palermo M, et al. Reduction of serum testosterone in men by licorice. N Engl J Med 1999;341:1158.
16. Health Canada. Drugs and Health Products. Licorice. Available: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod /monograph/mono_licorice-reglisse_e.html (accessed 2008 Sept 19).

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