Licorice Ingestion; An Unusual Cause of Rhabdomyolysis and Acute Renal Failure

Meyan Kökü; Rabdomyoliz ve Akut Böbrek Yetmezliğinin Beklenmeyen Bir Nedeni

Ramazan DANIŞ[1]
Çağlar RUHİ[1]
Nuh BERKETOĞLU[2]
Ali Veysel KAYA[2]
Barış YILMAZER[3]
Sedat KAYA[4]

1 Diyarbakır Training and Research Hospital, Department of Nephrology, Diyarbakır, Turkey
2 Diyarbakır Training and Research Hospital, Department of Internal Medicine, Diyarbakır, Turkey
3 Diyarbakır Training and Research Hospital, Department of Rheumatology, Diyarbakır, Turkey
4 Diyarbakır Training and Research Hospital, Department of Anesthesiology and Reanimation, Diyarbakır, Turkey

ABSTRACT

Licorice root has glycyrrhizic acid as the active ingredient and is responsible for a primary hyperaldosteronism-like syndrome with hypokalemia, metabolic alkalosis, and hypertension, typically accompanying low aldosterone. Herein, we present a rare complication of licorice consumption with acute renal failure.

A 49-year-old male patient was admitted to emergency department with generalized muscle pain/weakness, nausea, and dark urine. He was suffering from confusion and somnolence and the general condition was moderate. At laboratory assessment, potassium was 2.3 mEq/L, sodium 141 mEq/L, urea 146 mg/dl , creatinine 6.24 mg/dl, and total creatine kinase 4597 U/L. He had metabolic alkalosis (pH 7.59, HCO^{3-} 37.2 mmol/L). Hemodialysis was performed because of uremic neurological symptoms. His detailed anamnesis revealed consumption of herbal medication for the last 1.5 years to treat gastric complaints. The herbal medication included 16 gr licorice root powder (~600-750 mg glycyrrhizic acid) per 100 gr. The plasma aldosterone concentration was significantly suppressed [1.6 pg/ml (normal; 38.1-300 pg/mL)]. Under these conditions, our final diagnosis was hypokalemic rhabdomyolysis and acute renal failure due to licorice ingestion.

We present a rare life-threating effect of licorice ingestion in this report. Furthermore, we want to draw attention to the importance of a detailed medical history, including the use of herbal medications and regional traditional characteristics to confirm the diagnosis.

KEY WORDS: Licorice, Rhabdomyolysis, Acute renal failure

ÖZ

Meyan kökü; Güneydoğu Anadolu'da geleneksel bir içecek olmasının yanı sıra gıda/bitkisel ilaç endüstrisinde kullanılır. Aktif maddesi gliserizik asittir, primer hiperaldestronizim benzeri tablo ile hipokalemi, metabolik alkaloz ve hipertansiyona neden olabilir. Bu olgu sunumunda meyan köküne bağlı gelişen, literatürde nadir olan, bir rabdomiyoliz ve akut böbrek yetmezliği olgusu sunulmuştur.

49 yaşında erkek; kas güçsüzlüğü/ağrısı, bulantı, idrarda koyulaşma yakınmaları ile acil servise başvurdu. Fizik muayenesinde bilinç bulanıklığı ve uykuya meyil vardı. Hastanın laboratuvar bulguları; potasyum 2,3 mEq/L, sodyum141 mEq/L, üre 146 mg/dl, kreatin 6,24 mg/dl, total kreatin kinaz 4597 U/L idi, ayrıca metabolik alkalozu (pH 7,59, HCO^{3-} 37.2 mmol/L) mevcuttu. Hasta üremik nörolojik bulguları nedeniyle hemodiyalize alındı. Bilinç durumu düzelince alınan detaylı anamnezde yaklaşık 1,5 yıldır mide yakınması nedeniyle bitkisel ilaçlar kullandığı ve bitkisel ilacın 100 gr'nın 16 gr meyan kökü (~600-750 mg gliserizik asit) içerdiği öğrenildi. Bu bulgular ışığında kesin tanımız; meyan kökü alımına bağlı hipokalemi, rabdomiyoliz ve akut böbrek yetmezliği oldu. Hastanın plazma aldosteron düzeylerindeki baskılanma da tanımızı destekler nitelikteydi [1,6 pg/ml (normal; 38,1-300 pg/ml)].

Bitkisel ilaçlar ve gıda endüstrisinde yaygın olarak kullanılan meyan kökü yaşamı tehdit edici düzeyde akut böbrek yetmezliğine neden olabilir. Ayrıca bu olgu doğrultusunda hekimlere, bitkisel ilaçlar ve yöresel gelenekleri içeren detaylı anamnez alınmasının, tanıdaki öneminin vurgulanması amaçlanmıştır.

ANAHTAR SÖZCÜKLER: Meyan kökü, Rabdomiyoliz, Akut böbrek yetmezliği

Received : 31.08.2013
Accepted : 08.02.2014

Correspondence Address:
Çağlar RUHİ
Diyarbakır Eğitim ve Araştırma Hastanesi, Nefroloji Bölümü, Diyarbakır, Turkey
Phone : +90 533 560 38 81
E-mail : drcglr@gmail.com

INTRODUCTION

The herbal products and medications have widespread use, Unfortunately, it is not always possible to determine and control the quantity of their ingredients. Users and physicians rarely consider about their safety and side effects. Licorice root is used as a traditional syrup in the Southeastern Region of Turkey. Glycyrrhizic acid is the active ingredient of the licorice and responsible for the metabolic syndrome that mimics primary hyperaldosteronism. The primary symptoms of this syndrome are hypokalemia, hypertension, metabolic alkalosis, and typically low aldosterone concentration (1, 2). Licorice induced hypokalemia is usually mild but it may cause rhabdomyolysis followed by acute renal failure as previously shown in rare case reports (3).

Herein, we represented a patient with hypokalemia, metabolic alkalosis, rhabdomyolysis, and acute renal failure due to licorice consumption that necessitated hemodialysis. This is the first case with acute renal failure due to licorice reported from Turkey to the best of our knowledge and one of the rare cases in the literature. In addition, it indicates the importance of obtaining a detailed patient history that includes geographical and habitual differences, which may assist the treating physician in making the correct clinical diagnosis.

CASE PRESENTATION

A 49-year-old male patient was admitted to the emergency department with complaints of generalized muscle pain and weakness, numbness at the corners of mouth, nausea, and darkening of urine. He had no medical history of chronic disease, except for gastrointestinal complaints. There was no drug abuse or substance addiction history. Upon first physical examination at the emergency department, his general condition was moderate with accompanying cachexia. He was suffering from confusion and somnolence, blood pressure was 120/80 mmHg, heart rate 96 beats/min, respiratory rate 16/min and body temperature 37.3°C. There was generalized muscle weakness, without paralysis and sensory/motor deficit. Other systemic and neurologic examinations were normal. The first laboratory assessment results were sodium 141 mEq/L, potassium 2.3 mEq/L, calcium 8.2 mg/dl, phosphorus 8.7 mg/dl, AST 53 U/L, LDH 527 U/L, urea 146 mg/dl , creatinine 6.24 mg/dl , and total creatine kinase 4597 U/L. He had metabolic alkalosis with a pH value of 7.59 and HCO^{3-} value of 37.2 mmol/L. The urine examination and hemogram were normal.

The patient was hospitalized to the nephrology clinic due to an initial diagnosis of hypokalemia-induced rhabdomyolysis and acute renal failure. One session of hemodialysis was performed for 2 hours with a dialysate that contained sodium 145 mM/L, potassium 3 mM/L, calcium 1.75 mM/L and HCO^{3-} 24 mM/L because of the uremic neurological symptoms. On the next day of hospitalization, after one session of hemodialysis, his conscious state improved and a detailed medical history could be obtained. The patient stated that he had been using herbal products for 1.5 years to treat gastric complaints and had drunk twice the regular dose before admission to hospital. The patient's relatives were asked to bring a sample of product and we found that it contained 16 gr licorice root powder per 100 gr of product .We estimated that 16 gr of licorice root powder contains about 600-750 mg glycyrrhizic acid. The thyroid function tests, adrenal MRI, and other examinations, which were done in terms of the differential diagnosis of his hypokalemia and rhabdomyolysis, were normal. The urine electrolytes could be examined at the third day of hospitalization [potassium 31.2 mM/L (25-125 mM/L) and chloride 17.3 mM/L (110-250 mM/L)]. Our final diagnosis was hypokalemic rhabdomyolysis and acute renal failure due to licorice root ingestion. Furthermore, the plasma aldosterone concentration was significantly suppressed [1.6 pg/ml (normal; 38.1-300 pg/mL)], supporting our diagnosis.

Treatment of the patient was hydration with 0.9% isotonic saline, potassium replacement (7.5% KCl, 10 ml ampule, 12-18 ampules daily, adjusted according to the plasma potassium concentration) and the potassium-sparing diuretic of spironolactone 100 mg/day. The clinical symptoms and general condition of patient improved with this treatment in the following days. All of the laboratory parameters normalized within 9 days and he was discharged from hospital with recommendations of ceasing licorice intake, spironolactone 100 mg/day and outpatient follow-up one week later. He was asymptomatic and had normal renal functions at the follow-up. Table I represents the laboratory follow-up of the patient from admission to the emergency department to the outpatient visit.

DISCUSSION

This report presents a 49-year-old male patient who was admitted to the emergency department and finally diagnosed as licorice-induced rhabdomyolysis and acute renal failure. Although there are several case reports about licorice-induced hypokalemia and rhabdomyolysis (4, 5), acute renal failure that necessitates hemodialysis is very rare and this is the first report from Turkey.

Chronic licorice ingestion is already known to mimic the clinic of excess mineralocorticoid activity with symptoms of hypokalemia, metabolic alkalosis, and hypertension (1). However, hypertension has not been observed in all patients as previously mentioned in several cases similar to our report (3, 6). The typical feature of this "pseudohyperaldosteronism" is the low concentration of aldosterone (2). The pathogenesis of the disorder depends on the active ingredient glycyrrhizic acid in the licorice. It inhibits the renal 11-B-hydroxysteroid dehydrogenase type 2, which promotes the conversion of cortisol to cortisone (7, 8). Cortisol has mineralocorticoid activity; the excess renal cortisol binds to the mineralocorticoid receptor as aldosterone. The absolute effect is pseudohyperaldosteronism syndrome with suppressed aldosterone levels and renin activity, due to negative feedback of renin-angiotensin II loop (9).

Table I: Laboratory results of the patient during follow up.

	Reference interval	Day 1	Day 3	Day 5	Day 7	Day 9	Week 2
Urea	10-50 mg/dl	119	93	66	16	16	46
Creatinine	0.4-1.2 mg/dl	6.64	3.03	1.28	0.82	0.62	1.15
Potassium	3.5-5.2 mmol/L	2.3	2.43	3.14	3.42	3.6	3.42
Sodium	136-145 mmol/L	141	139	141	144	140	146
Creatinine kinase	26-308 U/L	4597	3175	3067	1152	291	346
PH	7.35-7.45	7.59	7.46		7.41		
Bicarbonate	22-26 mmol/L	37.2	29		26		
Aldosterone	38.1-300 pg/mL	1.6					

A urine potassium of >30 mmol/L usually suggest renal potassium loss and low urine chloride suggests hyperaldosteronism (10). In our patient, with the clinical picture and symptomatology of hyperaldosteronism, the relatively high urine potassium with low urine chloride additionally supported our diagnosis. Although we could not examine the plasma renin activity due to technical issues, the normal adrenal MRI and very low aldosterone concentration excluded primary hyperaldosteronism. Other possible causes of pseudohyperaldosteronism that include Cushing's syndrome, Liddle syndrome, and the syndrome of apparent mineralocorticoid excess were excluded (11) because of incompatible clinical/biochemical findings and recovery of the patient rapidly after withdrawal of licorice. 11-B-hydroxysteroid dehydrogenase activity shows variations among individuals, possibly due to genetic differences. Therefore, the severity and onset of symptoms attributable to licorice ingestion are related to the individual susceptibility as well as the duration of use and the dose (12). Although there are reports on symptomatic pseudohyperaldosteronism with small amounts of glycyrrhizic acid in a chewing gum (13), there are also reports with ingestion of quite large amounts. Celik et al reported a patient from the same region of Turkey as ours with hypokalemia, edema, and thrombocytopenia due to 200-500 mg daily glycyrrhizic acid consumption as a traditional beverage in our region (6). Since our patient had been drinking licorice root as either a beverage or herbal medication for 2 years, it was not quite possible to determine the definite glycyrrhizic acid dose. The day before the admission to hospital, he had a history of ingestion of one liter of herbal medication that contains 16 gr licorice root powder. We estimated that it contained about 600-750 mg glycyrrhizic acid and the reason for the critical condition of our patient was probably the regular consumption for a long time and the quite high last dose.

There is an increasing trend towards alternative medicines and herbal products in Turkey, as in many countries. However, this trend leads to a problematic issue as these products are widely accessible, sold without control of healthcare organizations, and the amount of ingredients are unclear. Physicians and healthcare organizations should be aware of the possible harmful effects of the regional food and beverage traditions, as mentioned in our article.

In conclusion, we presented a rare life-threating effect of licorice ingestion in this report: acute renal failure accompanied with hypokalemia and rhabdomyolysis. Furthermore, we would like to draw attention to the importance of obtaining a detailed medical history, including the use of herbal medications and regional traditional characteristics to confirm the diagnosis.

REFERENCES

1. Farese RV Jr, Biglieri EG, Shackleton CH, Irony I, Gomez-Fontes R: Licorice-induced hypermineralocorticoidism. N Engl J Med 1991;325:1223-1237
2. Kusano E: How to diagnose and treat a licorice induced syndrome with findings similar to that of primary hyperaldosteronism. Intern Med 2004;43:5-6
3. Velickovic-Radovanovic RM, Mitic B, Kitic D, Kostic S, Cvetkovic T, Djordjevic V: Acute renal failure after licorice ingestion: A case report. Central European Journal of Medicine 2011;6:113-116
4. Shah M, Williams C, Aggarwal A, Choudhry WM: Licorice-related rhabdomyolysis: A big price for a sweet tooth. Clin Nephrol 2012;77(6):491-495
5. Zenone T, Blanc Q: Rhabdomyolysis with major hypokalemia secondary to chronic glycyrrhizic acid ingestion. Rev Med Interne 2009;30(1):78-80
6. Whorwood CB, Sheppard MC, Stewart PM: Licorice inhibits 11 betahydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action. Endocrinology 1993;132:2287-2292

7. Kenouch S, Coutry N, Farman N, Bonvalet JP: Multiple patterns of 11 beta-hydroxysteroid dehydrogenase catalytic activity along the mammalian nephron. Kidney Int 1992;42:56-60
8. Stewart PM: Tissue-specific Cushing's syndrome, 11beta-hydroxysteroid dehydrogenases and the redefinition of corticosteroid hormone action. Eur J Endocrinol 2003;149(3):163-168
9. Draper N, Stewart PM: 11 Beta-hydroxysteroid dehydrogenase and the pre-receptor regulation of corticosteroid hormone action. J Endocrinol 2005;186:251-271
10. Rose BD: Clinical physiology of acid-base and electrolyte disorders. (4th ed) New York:McGraw-Hill;1994;515-517
11. Ferrari P, Lovati E, Frey FJ: The role of the 11beta-hydroxysteroid dehydrogenase type 2 in human hypertension. J Hypertens 2000;18(3):241-248
12. De Klerk GJ, Nieuwenhuis MG , Beutler JJ: Hypokalemia and hypertension associated with use of licorice flavored chewing gum. BMJ 1997;314(7082):731-732
13. Celik MM, Karakus A, Zeren C, Demir M, Bayarogullari H, Duru M, Al M: Licorice induced hypokalemia, edema, and thrombocytopenia. Hum Exp Toxicol 2012;31(12):1295-1298