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## A Curious Case Acute Kidney Injury (AKI) and Hypokalaemia Due to Glycyrrhiza Glabra (Licorice Root)

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**How to cite this article:**

Lakshminarayana GR, Raghunath KV, Sahiba E Ummer *et. al.* / A Curious Case Acute Kidney Injury (AKI) and Hypokalaemia Due to Glycyrrhiza Glabra (Licorice Root). *Urology, Nephrology and Andrology International*. 2020;5(2):61–63.

**Abstract**

The plants and its products are extensively used as source of medicines in Ayurveda, Siddha and traditional Chinese medicine. Even though rarely reported, adverse effects do occur with these types of medications. We report here an interesting case of AKI and hypokalaemia due to Kooshmandaswarasa ghrutham containing Benincasa Cerifera, Glycyrrhiza glabra and cow's ghee which was used for epilepsy. The Glycyrrhiza glabra, containing glycyrrhizin is the most likely culprit for causing AKI.

**Keywords:** Glycyrrhiza glabra; Licorice; Glycyrrhizin; AKI; Hypokalaemia.

**Introduction**

Plants have been an important sources of medicines since the beginning of human cultivation. There is a growing demand for plant based medicines, health products, pharmaceuticals, food supplements, cosmetics. Glycyrrhiza glabra (Figure 1) is a flowering plant of the bean family Fabaceae, it grows best in subtropical climates in deep, fertile, well drained soils, with full sun. Glycyrrhiza glabra is commonly known as Yashtimadhuh. Madhuka (Sanskrit) Jashtimadhu, Jaishbomodhu (Bengali) Jethimadhu (Gujarat) Jothimadh, Mulhatti (Hindi) Yastimadhuka, atimaddhura (Kannada) Iratimadhuram (Malayalam), Jeshtamadha (Marathi), Jatimadhu (Oriya), Atimaduram (Tamil), Atimadhuranu, Yashtimadhukam (Telugu), Licorice, Liquorice, Sweet wood (English). The extracts of Glycyrrhiza glabra is a popular sweetener found in many soft drinks, food products, snacks and is also extensively use in as part in herbal medicines.<sup>1,2</sup> The name Glycyrrhiza is derived from

the ancient Greek term 'glykos', meaning sweet, and 'rhiza', meaning root.<sup>2</sup> The licorice and its extracts are used as treatment in multiple diseases (gastric ulcers, postural hypotension, Addison's disease, HBV infection, beneficial effect of licorice gargle in reducing the risk of postoperative sore throat, decrease the risk of hyperkalemic arrhythmias in patients on chronic dialysis, adjuvant therapy of hirsutism and PCOS) in alternative forms of Medicine.<sup>2</sup> Its effect on Prostate, breast, colon, liver and lung cancer cell lines have also been under evaluation.<sup>2</sup> Professionals prescribing it and those using licorice and products need to know regarding the potential adverse effects, unlike the present case.

**Chemistry**

Glycyrrhizin, a triterpenoid compound, accounts for the sweet taste of licorice root and represents a mixture of potassium–calcium–magnesium salts of glycyrrhizic acid.<sup>2</sup> The content of glycyrrhizin

in licorice roots varies from 2 to 25%, depending on the particular species.<sup>2</sup> Glycyrrhizin is 200-250 times sweeter than sucrose and its sweetness has a slower onset than sugar but persists in the mouth for a longer time.<sup>3</sup> Glycyrrhizic acid has an action resembling that of mineralocorticoids.<sup>2,3</sup> The glycyrrhizin mimics mineralocorticoids by blocking 11-beta hydroxy steroid dehydrogenase 2 and also avidly binding to mineralocorticoid receptors similar to aldosterone. Studies have also shown that licorice also has significant antioxidant activity & estrogen-like activity due to presence of hispaglabridins A / B & glabridin / glabrene respectively.<sup>2,3</sup>

### Case Report

A male aged 20-year, case of epilepsy since childhood on Oxcarbazepine 300 mg BID and Clobazam 5 mg BID, was referred to our centre from another hospital with worsening renal parameters, reducing urine volume, and edema since 2 days recently (November 2020). He gave history of treatment with Kooshmandaswarasa ghrutham (Contents - Benincasa Cerifera 79.75 mg, Glycyrrhiza glabra 1.18 gm and Cow's ghee 10 ml in every 10 ml) for epilepsy (figure 2). The Kooshmandaswarasa ghrutham was administered for 4 days at dose of 30 ml on day 1, 60 ml on day 2, and 100 ml (in empty stomach) on day 3 & 4, till 2 days prior to present admission to our centre. There was no vomiting, diarrhoea, fever, myalgia, undue physical exertion, any other medication intake, or any significant pointers towards etiology of his AKI in history. He had minimal pedal edema with BP of 126/84 mmHg, heart rate 92 beat/min, respiratory rate 16/min, and body temperature 38°C. The patient was cooperative, oriented and systemic examination was unremarkable.

His evaluation showed severe renal failure (S. Creatinine: 3.9 mg/dl & Blood urea: 100 mg/dl), urine routine was normal. His serum creatinine was 0.6 mg/dl, 2 months during routine Neurology follow-up. His other reports were; Hemoglobin: 12.9 g/dl, WBC count: 10500 c/cmm, platelets: 3, 20,000 c/cmm, serum sodium: 126 mmol/l, potassium: 3.3 mmol/l, RBS: 112 mg/dl, C3: 137.37 mg/dl, C4: 25.45mg/dl. ABG showed mild metabolic acidosis (pH 7.3, PCO<sub>2</sub> 36 mmHg, HCO<sub>3</sub> 24 mmol/L, pO<sub>2</sub> 95 % & SPO<sub>2</sub> 98%) and normal CPK, His ultrasound abdomen revealed bilateral bulky kidneys (Right 10.8x 5.5 cm and Left 11.2 x 5.6 cm) with increased echogenicity, normal PCS, urinary bladder and prostate. The need for renal biopsy was explained to the patient's bystanders for further evaluation of

AKI, but they weren't willing.

He was treated with empirically IV Methylprednisolone 250 mg OD (5mg/kg/day) × 3 days, followed by Prednisolone 30 mg/day, oral potassium supplements (20 mEq × 8 hourly), Furosemide, Pantoprazole, with suspicion of acute interstitial nephritis, due to Glycyrrhiza glabra. The Oxcarbazepine 300 mg BID and Clobazam 5 mg BID were continued and Kooshmandaswarasa ghrutham was stopped. His serum creatinine started improving with treatment from 3.9 to 0.68 mg/dl (3.9→2.78→0.88→0.68 mg/dl) (Figure 3) with good urine output & also his serum potassium improved to 4 mEq/L. He was discharged after 5 days with an advice to continue antiepileptics, Prednisolone and review after 1 week.



Fig. 1: Glycyrrhiza glabra: plant and its roots.



Fig. 2: Kooshmandaswarasa ghrutham and its contents used by our patient.

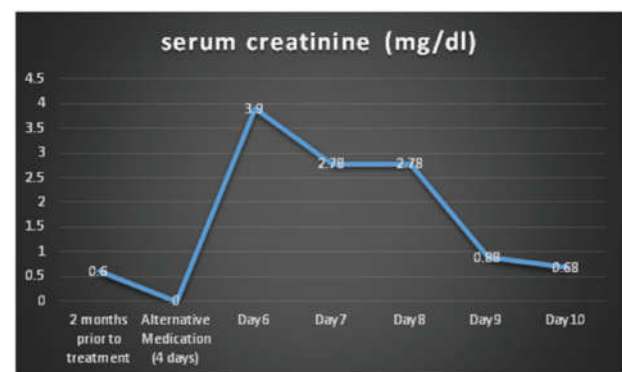


Fig. 3: Serum Creatinine profile of the patient - temporal profile.

## Discussion

Licorice overconsumption or unmonitored prescription has associated number complications has been well discussed an article titled Licorice abuse: time to send a warning message, by Irina Komarova et al, which mainly included hypertension, hypokalaemia, muscle weakness, and rarely rhabdomyolysis.<sup>2</sup>

However, there scarce literature regarding its renal adverse effects (hypokalaemia and rhabdomyolysis, acute renal failure) limited only to few case reports.<sup>4-10</sup> Scarce literature also limits at our ability arrive at potential pathogenetic mechanisms, therapeutic / toxic dose, pathology, and treatment protocols.

This report presents a 20-year-old male patient who was admitted with hypokalaemia and AKI due to an ayurvedic medicine containing Glycyrrhiza glabra & is the first case to be reported from India, who was managed successfully with IV Methylprednisolone, followed by Prednisolone, oral potassium supplements, diuretics and supportive measures. Although a renal biopsy could not be done in our case, it revealed severely damaged tubular cells with intense vacuolar formation in one of the earlier case.<sup>10</sup>

The AKI was mostly associated with hypokalaemia, rhabdomyolysis induced muscle injury, elevated CPK in previously reported cases. There was evidence of rhabdomyolysis induced muscle injury, suggesting an alternative mechanism for AKI like acute interstitial nephritis (AIN). The therapeutic response and temporal profile of improvement also points towards AIN.

## Conclusion

Glycyrrhiza glabra / Licorice is extensively used production of plant based medicines due to its anti-oxidant, anti-apoptotic, anti-thirst, properties, pro-estrogen and some unknown properties in multiple diseases. It's used as artificial sweetener in food supplements due to taste. Glycyrrhiza glabra / Licorice toxicity must be considered as a causative factor in unexplained hypokalaemia, AKI especially in those consuming medications from Alternative Medicine like Ayurveda, Siddha

or traditional Chinese Medicine. The effects of licorice are reversible upon cessation and proper treatment, based on the duration and dose of its consumption. We need further studies to design proper protocols for its evaluation & treatment.

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