Tribulus terrestris-induced severe nephrotoxicity in a young healthy male

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Abstract
Herbal medications are being progressively utilized all over the world. Nevertheless, herbal remedies are not without hazards and several cases of adverse reactions have been described. Tribulus terrestris is traditionally used because of its aphrodisiac and antiurolithiatic activities with almost complete inhibition of stone formation. We report a case of T. terrestris-induced hepatotoxicity, nephrotoxicity and neurotoxicity in an Iranian male patient who used the plant’s extract to prevent kidney stone formation. He presented with seizure and very high serum aminotransferases and creatinine after consuming herbal water for 2 days. Discontinuation of the herbal remedy resulted in improvement in symptoms and normalization of his liver enzymes.

Keywords: clinical pharmacy; hepatotoxicity; nephrotoxicity; neurotoxicity; Tribulus terrestris

Background
Herbal remedies are used with the assumption that herbal medicines are natural and safe to use. However, the literature abounds with reports of their adverse effects [1]. Tribulus terrestris has a worldwide distribution. Its roots, seeds, fruits and leaves had been traditionally used for therapeutic purposes, in particular urolithiasis [2,3]. There were some reports of hepatorenal syndrome and neurotoxicity in goats and sheep grazing on T. terrestris [4,5], but to our knowledge, this is the first report of human adverse reactions. We present a patient who consumed T. terrestris and presented with acute kidney injury, hepatitis and seizure. Cessation of the herb along with dialysis resulted in a full recovery.

Case report
A 28-year-old man was referred to Imam Khomeini Hospital for investigation of renal, hepatic and neurologic dysfunction. Two days prior to admission, he started taking T. terrestris water bought from a grocery without taking any other medication. The only finding in his past medical history was passing kidney stones two times, 10 and 7 years ago, respectively. He does not smoke nor consume alcohol. The grocer recommended T. terrestris water instead of drinking water, so the patient consumed 2 L of it in two consecutive days. He was admitted with two episodes of seizure preceded by severe weakness in the lower limbs, malaise and poor appetite. His vital signs were normal except for rising blood pressure (BP) to 180/110 mmHg. He was advised to discontinue T. terrestris water. His BP declined to 160/110 mmHg by amlodipine 10 mg daily, captopril 25 mg and prazosin 1 mg thrice daily and furosemide 60 mg four times per day. Thereafter, prazosin was replaced by minoxidil 2.5 mg twice daily that resulted in a BP of 130/85 mmHg. Blood tests showed impaired renal function with serum creatinine (SCr) and urea nitrogen concentration of 17.4 and 141 mg/dL (1538.16 μmol/L, 50.34 mmol/L), respectively. Accordingly, haemodialysis was started. His liver function tests showed elevated serum aminotransferases up to more than 40 times of the upper limits of normal. The urine analysis indicated mild proteinuria of 0.28 g/day, sterile pyuria and haematuria. The 24-h urine revealed sodium concentration of 20 mmol/L. Although clinical pharmacists did not agree, the neurologist prescribed phenobarbital 100 mg daily and an extra dose of 50 mg after each dialysis. Phenobarbital dosage was adjusted to 100 mg after each haemodialysis by the clinical pharmacist. Patient’s blood and urine cultures were negative repeatedly. Viral hepatitis, autoimmune diseases, leptospirosis, endocarditis and heart failure all were ruled out. Abdomen and pelvis computed tomography without contrast media revealed a presence of at least two small gravels in mid-left kidney. Left ureteral dilation with a 5- to 6-mm stone was seen.

Seven days after cessation of herbal remedy, patient’s hepatic function improved spontaneously to serum alanine aminotransferase level of 52 U/L. Due to slow resolution of kidney function, at this time, prednisolone 60 mg/day was started. Ten days after prednisolone initiation, the patient experienced low levels of BP; therefore, the antihypertensive management was started with amlodipine and furosemide. Blood pressure declined to 130/85 mmHg. Due to slow resolution of kidney function, at this time, prednisolone was continued. After 10 days, patient’s liver enzymes normalized. His renal function improved to SCr and urea nitrogen concentration of 2.4 and 15 mg/dL (218.4 μmol/L, 5.25 mmol/L), respectively. His BP declined to 120/80 mmHg by amlodipine 10 mg daily and furosemide 40 mg three times per day. Blood tests showed normal liver function with serum aminotransferase and creatinine level of 47 U/L and 1.4 mg/dL (83.1 μmol/L), respectively. He was discharged on prednisolone 0.3 mg/kg daily. After 2 months, his BP declined to 110/70 mmHg by valsartan 160 mg daily and furosemide 40 mg three times per day. His BP is stable on antihypertensive management with no signs of recurrence.

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pertensive medications were stopped one after another. Five days later (22 days after cessation of herbal remedy), his SCr decreased to 1.8 mg/dL (159.12 μmol/L) and urine analysis became negative for both haematuria and pyuria. All medications were stopped, except for prednisolone that was tapered down to 15 mg/day. He was discharged with a prednisolone tapering plan and referred to the urology clinic 2 weeks later with prednisolone dose of 5 mg daily.

Discussion

_T. terrestris_ is widely used because of its antiurolithiatic activity. Hepatitis, nephrotoxicity, neurotoxicity and hepatorenal syndrome have been reported in animals feeding on _T. terrestris_. Our patient consumed a great amount of the herb’s water for 2 days. His first presentation was severe weakness followed by two episodes of seizure. _T. terrestris_ extract showed CNS stimulant activity at a dosage of 20 mg/kg in rats [6] and motor neuron disease in animals. The _Tribulus_ toxin causes progressive astrocytes’ degeneration, glutamatergic neuronal excitation reduction and decreases subthalamic nucleus normal excitatory function [7]. This adverse effect has not been observed in humans yet. The consumption of this herb had resulted in elevated serum aminotransferases, creatinine and urea that could be attributed to possible hepatorenal syndrome, acute interstitial nephritis (AIN) or acute tubular necrosis (ATN). The new diagnostic criteria of hepatorenal syndrome is the presence of ascites, elevated SCr (>1.5 mg/dL or ~132.6 μmol/L) and urine analysis revealed haematuria. Thus, the patient would not fulﬁl the diagnostic criteria of hepatorenal syndrome [8]. In contrast to our patient’s condition, AIN typically is unaccompanied by oliguria or dialysis requirement [9]. Although it usually occurs 2 weeks after exposure to an offending agent, AIN may happen sooner upon previous exposure to a chemically similar agent [9]. The patient denied any herbal or chemical consumption. AIN renal manifestations include sterile pyuria with eosinophiluria and low-grade proteinuria [9]. The patient’s urine analysis was negative for eosinophiluria. Patients with ATN present with kidney injury usually after prolonged exposure to offending agent, may be oliguric or require dialysis, with increased sodium fractional excretion (1.3% in our patient) and probable mild proteinuria. Causative agent cessation, hydration and haemodialysis could result in recovery in most cases [9]. Therefore, our patient’s symptoms were most consistent with ATN. Renal biopsy was required for certainty but could not be performed due to the patient’s hydronephrosis along with his morbid obesity.

Our patient’s urinalysis was consistent with tubular dysfunction and there was no manifestation of glomerular disease, i.e. few WBCs and RBCs as well as proteinuria and no detectable casts. Due to short-term use of this herb, we anticipated a good prognosis for our patient. In reality, the creatinine level stabilized, the urine output improved and his symptoms disappeared. In conclusion, herbal remedy may elicit some toxicity that could progress to end stage if the diagnosis was not made early or if he continued _T. terrestris_ consumption.

Conflict of interest statement. None declared.

References


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