No pain, no gain – exercise-induced rhabdomyolysis associated with the performance enhancer herbal supplement ephedra

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Summary

Background: We describe a rare case of severe rhabdomyolysis provoked by ingestion of a performance-enhancer herbal supplement containing ephedra.

Case Report: A healthy 21-year-old Army soldier complained of “complete muscle failure” after collapsing at the end of Army Physical Fitness Test. The patient was found to be tachycardic and hypotensive, but his vital signs quickly stabilized after receiving sodium chloride in the ambulance. Physical examination of the patient, including a thorough neuromuscular exam, was unremarkable. Urine tested positive for myoglobin. Initial creatinine kinase was 426 U/L, which increased to a maximum creatinine kinase of 241,418 U/L by hospital day 6. The patient also developed acute renal failure secondary to pigment-induced acute tubular necrosis. He was treated with bicarbonate-containing fluid. The patient’s creatinine kinase and renal function had normalized at one month follow-up. A muscle biopsy was negative for underlying neuromuscular disease. His past medical history was only notable for the patient having taken 2 tablets of an herbal supplement containing ephedra every day for a month leading to his physical fitness test.

Conclusions: Rhabdomyolysis and myoglobinuric renal failure associated with ephedra use are a very uncommon occurrence, but a significant clinical event that should be closely monitored due to rampant use by young adults of ephedra-containing dietary supplements.

key words: ephedra • dietary supplement • exercise • drug abuse • creatinine

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CASE REPORT

A healthy 21-year-old Army soldier presented to the Emergency Department of a Military Medical Center complaining of “complete muscle failure” after collapsing at the end of the 2-mile run of the Army Physical Fitness Test (APFT). Of note, he reported taking 2 minutes off of his usual two-mile run time. The patient had no prior difficulty with the fitness test. The APFT test took place on a cool October morning with an ambient temperature of 73°F. In the field, the patient was found to be tachycardic (with heart rates in the 130s) and hypotensive (with systolic blood pressures in the 80s). After receiving 1L of 0.9% sodium chloride in the ambulance, his vital signs quickly stabilized. Upon admission in the emergency room and prior to any therapeutic intervention, his initial temperature was 99.2°F, and subsequent readings conducted every 8 hours during the patient’s hospital stay were within normal limits. His past medical history was only notable for the patient having taken 2 tablets of an herbal supplement containing 20 mg of ephedrine every day for a month prior to his APFT test including the morning of the test. Additional ingredients of Energel, as listed on the bottle label, were as follows: caffeine 90 mg, iodine 37.5 mcg, ginger root extract 25 mg, mustard seed 75 mg, meadowsweet powder 100 mg, guanana seed extract 250 mg, schisandra extract 8.3 mg, Indian turmeric extract 4 mg, and Siberian root powder 25 mg. The proprietary blend also contained soybean oil, gelatin, glycine, caramel color, titanium dioxide. Urine and serum drug screens performed upon admission revealed the patient was negative for illicit drugs, alcohol, salicylates, and acetaminophen. He admitted to drinking very little water over several months, even before taking the herbal supplement, because “too much fluid aggravated his heartburn”. His physical exam, including a thorough neuromuscular exam, was unremarkable and there was no indication of spontaneous muscle pain or muscle pain induced by pressure. The patient denied muscle pain or cramps and ambulated without assistance. Initial renal panel revealed: sodium 139 meq/l, potassium 4.5 meq/l, chloride 108 meq/l, bicarbonate 12 meq/l, BUN 15 mg/dl, creatinine 1.9 mg/dl, glucose 273 mg/dl, calcium 9.8 mg/dl, magnesium 5.1 mg/dl, and phosphorus 2.8 mg/dl. Liver function tests revealed: alkaline phosphatase 77 IU/L, aspartate aminotransferase 4150 U/L, alanine aminotransferase 1432 U/L, gamma-glutamyltransferase 41 IU/L, aldolase 1008 MU/ML. Urinalysis showed: hazy amber appearance, with specific gravity 1.007, pH 5.0, protein >300mg/dl, glucose negative, ketones trace, bilirubin negative, blood large, nitrite negative, leukocyte esterase negative [2,3] RBC/HPF, few uric acid crystals. Urine tested positive for myoglobin.

Initial creatinine kinase was 426 U/L, which increased to a maximum creatinine kinase of 241,418 U/L by hospital day 6 (Figure 1). The patient also developed acute renal failure secondary to pigment-induced acute tubular necrosis with a maximum serum creatinine of 2.4 mg/dl. He was treated with bicarbonate-containing fluid to maintain a urine output of 250 cc/hr. At one month follow-up the patient’s creatinine kinase and renal function had normalized. A muscle biopsy done 5 months after his initial presentation was negative for underlying neuromuscular disease.

DISCUSSION

Ma huang, the Chinese name for ephedra, has been used in China for over 5,000 years to treat asthma and upper respiratory infections. Today, ephedra-containing supplements are very popular as dietary aids and performance-enhancers. An estimated 12 million of these supplements were sold in the U.S. in 1999 [3]. Adverse cardiovascular events may arise from ephedra’s adrenergic effects and include acute myocardial infarction, severe hypertension, and lethal cardiac arrhythmias [2,3]. Ephedra has also been implicated in cases of hemorrhagic and thrombotic stroke via its hypertensive and vasoconstrictive actions [2,3]. Despite accounting for only 0.82% of herbal product sales in the United States, products containing ephedra were responsible for 64% of the adverse reactions reported to the Toxic Event Surveillance System of the American Association of Poison Control Centers [1]. A comprehensive review [3] of adverse events reported to the (FDA) revealed a total of 87 cases out of 140 that were likely linked to ephedra dietary supplement use. Based on a standardized rating system to assess for causation related to ephedra use, this study tallied 10 deaths and 13 cases of permanent impairment. Of note, two cases of rhabdomyolysis were attributed to an ephedra supplement use [3,4].

A small case series of three otherwise healthy athletes in their twenties, who developed acute renal failure and exercise-induced rhabdomyolysis after taking ephedrine containing dietary supplements, has also been reported [5]. Two of these patients developed thigh compartment syndromes requiring fasciotomies. All three were dehydrated.

Figure 1. Patient creatinine kinase levels during hospital course. Severe rhabdomyolysis is indicated by significantly increased creatinine kinase levels which reached maximum level on hospital day 6.
after participating in two days of strenuous outdoor exercise prior to hospitalization.

Our patient was similarly a well-conditioned athlete. He developed severe rhabdomyolysis after taking Energel, a performance-enhancing herbal supplement containing ephedra, for 1 month prior to his APFT. Volume depletion, due to limited water intake secondary to a history of gastroesophageal reflux disease, might have contributed to the severity of his response. Although, this mouth-breathing runner had a low grade oral temperature elevation, he could have been hyperthermic (another known cause of rhabdomyolysis) upon measurement of a core temperature. The central nervous system effects of ephedra, similar to those of amphetamine drugs, may also have played a role given the dramatic reduction of 2 minutes off of his usual run time without any psychic awareness of increased effort. The patient had none of the known risk factors associated with massive rhabdomyolysis (e.g., hypokalemia, hypothyroidism, impaired sweating, status asthmaticus, crush injuries, seizures, delirium tremens), except for taking medications (i.e., ephedra).

Millions of American athletes use over-the-counter dietary supplements including ephedra, adrenal or anabolic steroids, high dose creatine, which all have been linked to an increased risk of rhabdomyolysis [6,7]. Initially proposed in 1997, but later withdrawn in 2000, the FDA recommended taking no more than 24 mg of ephedrine equivalent for no more than seven consecutive days [8]. Despite these safety guidelines and initiatives from the FDA to regulate ephedrine and similar dietary supplements, large amounts (up to 1,000 tabs/bottle) of ephedra-containing herbal supplements remain readily available to consumers at health food stores and via internet sources. These are marketed to appeal to individuals with a broad variety of interests, including weight loss, performance enhancement, or obtaining an “herbal ecstasy” experience. Side effects are often seen after taking low doses [3] for longer than recommended durations.

Ephedra-containing supplements often also contain caffeine, as did the supplement our patient had taken (in an amount equivalent to more than 5 cans of caffeinated soda). Caffeine, in combination with ephedra, could augment the release of catecholamines [9]. In 46 controlled experimental studies of ephedra and caffeine supplements marketed for weight loss, the supplements have shown to lead to negligible versus only moderate alterations in heart rate and blood pressure [2,10–12]. Although a few studies support modest effects of ephedrine and caffeine on very short-term athletic performance [2], no studies to date have specifically assessed the effects of herbal ephedra-containing dietary supplements on athletic performance.

Our patient exemplified such a case of exercise-ephedra-induced rhabdomyolysis. The following factors might have contributed to the observed rhabdomyolysis: 1) severe arterial vasoconstriction leading to skeletal muscle ischemia and infarction, 2) increased intracellular calcium leading to muscle cell damage, 3) increased “metabolic stress” with increased oxygen consumption, 4) over-exertion secondary to central CNS effects. In addition, physiologic effects of ephedra parallel those seen in other sympathomimetic drugs, such as cocaine and the “club drug” Ecstasy, also known to cause rhabdomyolysis [13,14].

A broad range of athletes including military recruits, marathon runners, weightlifters, and poorly-conditioned amateurs have developed exercise-induced rhabdomyolysis even without the use of ephedra supplements [15]. Metabolic and cardiovascular stress in combination with exercise may be a predisposing factor for rhabdomyolysis. Because ephedra-related drugs have been shown to exacerbate metabolic and cardiovascular stress, a combination of exercise and ephedra may prove fatal. Accordingly, military soldiers, who are regularly subjected to rigorous exercise training and may seek performance-enhancement supplements, remain as one of the most vulnerable populations to the dangerous combination of exercise and ephedra.

The accessibility of over-the-counter ephedra supplements likely will increase the cases of rhabdomyolysis, among other side effects, in high performance athletes. The public is slowly becoming aware of the serious potential health risks of ephedra-containing, as well as other health supplements. The present report of a rare case of ephedra-exercise-induced rhabdomyolysis, together with a few other similar cases, warrants further vigilance among health care providers, as well as potential users of the supplements. Because military soldiers are high performance athletes, the need for better education about the risks of taking ephedra supplements among this population should be considered.

CONCLUSIONS

We report here a rare case of rhabdomyolysis and myoglobinuric renal failure associated with ephedra use. In April 2004, the FDA officially banned buying or selling of ephedra, and warned consumers not to take products containing the stimulant. However, by the following year in April 2005, a federal judge ruled against the FDA ban on ephedra stating that ephedra was wrongly being regulated by the FDA as a drug and not a food. Specifically, the federal law requires the FDA to prove that a dietary supplement is harmful, rather than having the manufacturer prove it is safe, as is required with drugs. This ruling in effect allows once again buying and selling of ephedra supplements. Although the present case of rhabdomyolysis is a very uncommon occurrence, the reversal of the FDA’s ban is likely to allow the widespread consumption of dietary supplements containing ephedra and its derivatives among young adults, especially soldiers and athletes who are seeking performance-enhancing drugs. The adverse side effects of ephedra-containing dietary supplements should be considered as a major public health concern.

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