Seizure Activity and Unresponsiveness after Hydroxycut Ingestion

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A 22-year-old man was hospitalized after unexplained seizure-like activity and unresponsiveness. A urine toxicology screen was negative for salicylates, acetaminophen, alcohol, and drugs of abuse. Medical history was insignificant with the exception of recent (within 2 wks) ingestion of Hydroxycut, a dietary supplement purported to be energy enhancing, muscle building, and fat burning. The agent contains ephedra alkaloids and caffeine, which are both central nervous system stimulants; the etiology of seizure was attributed to their consumption. Due to a significant number of reported adverse events, the United States Food and Drug Administration (FDA) proposed regulations for dietary supplements containing ephedra alkaloids and requested an independent review of case reports linked to these products. Because herbal products are not subject to the same rigorous FDA regulations required for prescription and over-the-counter products, consumers unknowingly risk adverse effects when taking these products. Questioning patients about consumption of herbal products should be part of routine medical visits.

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Alternative medicine, defined as medical interventions not included in medical school curricula or routinely offered in United States hospitals, is being used by an increasing number of people.[1, 2] Examples are herbal and homeopathic products, chiropractic therapy, hypnosis, spiritual healing, and acupuncture.[2, 3]

The market for herbal products has grown enormously over the past several years. It is estimated that more than half of the U.S. population uses herbal products, spending more than $3 billion annually.[4, 5] Consumers frequently self-medicate with herbal products to treat or prevent medical conditions and to improve or maintain overall well-being, believing these products to be free of adverse effects.

A recent national survey documented typical characteristics of Americans who use herbal products.[2] Their use was more frequent among women than men and less common among African-Americans compared with other racial groups. The highest rate of herbal product use was reported among people 35–49 years of age who are college educated and have an annual income over $50,000.

The U.S. Food and Drug Administration (FDA) defines dietary supplements as products that may contain vitamins, minerals, herbs, botanicals, and amino acids.[6] These products are available in an assortment of formulations, including teas, powders, tablets, capsules, and elixirs, and may be marketed as individual agents or in combination with other ingredients.[6, 7] In 1994, a separate classification was established for dietary supplements when the U.S. Congress passed the Dietary Supplement and Health Education Act (DSHEA). According to the DSHEA, herbal

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products, which are classified as dietary supplements, are not considered drugs; therefore, the FDA does not require the same evaluations of efficacy and safety that are required of prescription and over-the-counter agents.[3, 4] Because manufacturers of herbal products are less restrictively regulated than pharmaceutical manufacturers, inconsistent labeling and lack of safety data and quality control are concerns.[3, 6]

The lack of rigorous regulation of herbal products leaves both consumers and health care practitioners with little information about adverse effects of these products. Case reports are one of the few routes by which adverse effects are reported. We describe seizure activity and unresponsiveness in a young, healthy patient after several weeks of consumption of Hydroxycut (MuscleTech Research and Development, Inc., Brampton, Ontario, Canada), a combination of hydroxagen, guarana extract, L-carnitine, ma huang extract, willow bark extract, and chromium picolinate.[8]

Case Report

A 22-year-old, previously healthy, Caucasian man came to the emergency department after having questionable seizure activity and subsequent unresponsiveness. He had no significant medical or family history of seizures. He had been skiing during the day and was described by friends as being withdrawn and behaving peculiarly. While traveling home on a charter bus, the patient became agitated, combative, and had a seizure-like episode without tonic-clonic movements and became unresponsive. His eyes rolled back in his head, and he experienced bladder incontinence and frothing at the mouth. The duration of the seizure-like episode was not recorded. On arrival of a rescue squad, the patient was combative and only responsive to tactile stimuli. He was transported to the emergency department for further evaluation.

On arrival, the patient's blood pressure was 160/90 mm Hg, pulse 120 beats/minute, respiration rate 12 breaths/minute with 100% oxygen saturation, and temperature 36.3ºC. The patient's pupils were minimally reactive and 6 mm bilaterally. The patient continued to respond to tactile stimuli by withdrawing and being slightly combative. Because of his behavior, the patient was sedated, paralyzed, and intubated for airway protection. Except for unresponsiveness to verbal stimuli, physical examination was unremarkable. Laboratory values were within normal limits except for potassium 3.2 mEq/L (normal range 3.5–5.0 mEq/L) and phosphorus 1.8 mg/dl (normal range 2.5–5 mg/dl). A urine toxicology screen showed no salicylates, drugs of abuse, alcohol, or acetaminophen. A blood toxicology screen was not performed. The patient underwent chest roentgenogram, lumbar puncture, head computed tomography, and electroencephalogram (EEG), all of which had negative findings.

According to the patient's family and roommate, the man had been taking 12 or more tablets/day of a muscle-enhancing product called Hydroxycut for the past 2 weeks. Also, 3 days before admission, the patient had complained that he was experiencing fatigue, headaches, and shaking hands. It was not known when the last dose of Hydroxycut was consumed.

The patient underwent gastric lavage and received intravenous fluids before being admitted to the medical intensive care unit. A lorazepam infusion was started for sedation, and mechanical ventilation was continued. The patient also received sorbitol for gut decontamination and famotidine for stress ulcer prophylaxis. The lorazepam dosage was gradually decreased, but the patient remained unarousable for another day. To determine whether other sources of lethargy existed, an emergent EEG was performed, but seizure activity was not detected. A magnetic resonance imaging-magnetic resonance angiography (MRI-MRA) was done to rule out central nervous system (CNS) vasculitis possibly caused by caffeine or ephedrine. The patient was started on methylprednisolone 125 mg intravenously every 6 hours for suspected CNS vasculitis until results of the MRI-MRA were obtained. When results were normal, the event was attributed to Hydroxycut.

Two days after admission, the patient was arousable, and methylprednisolone was discontinued. By the third day, the patient was fully awake and conversant, without complaints of pain. However, he had no memory of the event. The patient seemed to be suffering from short-term memory loss and had difficulty remembering new people whom he had met. His cognitive deficit was attributed to residual effects of lorazepam. Two years after the event, the patient continues to be free of long-term adverse sequelae and has had no other admissions.

Although the product consumed by the patient was not obtained for laboratory analysis, this adverse drug reaction (ADR) was reported to our

Table 1. Ingredients of Hydroxycut (4 Capsules)[8]

		Active Ingredient		
Components	Amount (mg)	Compound	% of Component	Strength (mg)
Hydroxagen	2000	Hydroxycitric acid	50	1000
Guarana extract	910	Caffeine	22	200
L-Carnitine	100	L-Carnitine	100	100
Ma huang extract	334	Ephedra	6	20
Willow bark extract	100	Salicin	15	15
Chromium picolinate	0.3	Chromium picolinate	100	0.3

institution's ADR program and the MedWatch program of the FDA.

Discussion

Hydroxycut, a combination dietary supplement (Table 1), is marketed as an energy-enhancing, muscle-building, and fat-burning product. The recommended daily dose is 4 capsules with each meal, not to exceed 12 capsules/day.[8] Hydroxycut contains six different natural products, of which ma huang extract (6% ephedra) and guarana extract (22% caffeine) are the most likely to stimulate the CNS and cause seizures.

Ma Huang

Ma huang is an herbal product derived from the genus *Ephedra* and is a common ingredient in products marketed for weight control, energy augmentation, and respiratory function improvement. Ephedrine, pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine are ephedra alkaloids and are nonselective adrenergic agonists that stimulate the sympathetic nervous system.[9] Common adverse effects of ephedra alkaloids are nausea, vomiting, dizziness, tremor, anxiety, agitation, insomnia, and headache. This class of alkaloids can cause cardiac stimulation leading to severe hypertension, cardiac arrhythmias, myocardial infarction, and stroke.[9, 10]

Ephedrine-containing products have caused severe ADRs, including insomnia, nervousness, seizures, stroke, CNS vasculitis, premature ventricular contraction, myocardial infarction, and death.[11] In June 1997, the FDA proposed regulating the quantity of ephedra alkaloids that could be contained in dietary supplements. The proposed guidelines recommended limiting the amount to a maximum of 8 mg/dose, a cumulative intake of 8 mg within a 6-hour period, or a total consumption of 24 mg/day for no more than 7 days. The regulations also suggested prohibiting the addition of stimulants (such as caffeine) to any product that already contained ephedra alkaloids. If the ephedra alkaloid product promotes short-term excessive intake, then it also must contain a warning label that states, "Taking more than the recommended serving may result in heart attack, stroke, seizure, or death."[12, 13]

In August 1999, the FDA withdrew portions of its 1997 proposal and requested independent reviews of submitted ADRs. Its most recent proposal concerning ephedra alkaloids includes banning dietary supplements that combine these alkaloids with other stimulants; warning consumers that if they have certain health conditions or are taking certain drugs, the supplements should not be taken; and warning consumers to discontinue intake of the product if they develop any signs or symptoms,[14] including headache, dizziness, anxiety, tremor, and palpitations.[9, 10]

Independent reviews were conducted of 140 ephedra alkaloid-associated ADRs of the 273 submitted to the FDA between June 1, 1997, and March 31, 1999. Approximately 50% of the ADRs were cardiovascular in nature, and 18% involved the CNS. One-third of the reviewed ADRs established causality as definitely or probably related to consumption of supplements containing ephedra alkaloids, whereas another one-third was classified as possibly related. Several of the reactions resulted in death or permanent disability.[15] The FDA plans to finalize the proposed restrictions on ephedra alkaloids after obtaining public input.[14] The severity of the ADRs and their association with ephedra alkaloids may expedite implementation of regulations.

Caffeine

Caffeine has long been recognized as having

Table 2. Application of Naranjo Scale[27] to Patient

Causality Assessment	Yes	No	Do Not Know
1. Are there previous conclusive reports on this reaction?	+1[a]	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2[a]	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1[a]	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0[a]
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2[a]	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0[a]
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0[a]
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0[a]
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0[a]	0
10. Was the adverse event confirmed by any objective evidence?	+1	0[a]	0
Patient's score: 6			

[a]Patient's response.
Scoring system: ≥ 9 = definite adverse drug reaction; 5–8 = probable; 1–4 = possible; ≤ 0 = doubtful.

central stimulant properties producing numerous pharmacologic responses including CNS and cardiovascular system stimulation, smooth muscle relaxation, catecholamine release, and metabolic activity increase.[16] Documented CNS effects that are produced by caffeine are increased alertness, decreased psychomotor reaction time, and prolonged wakefulness. Acute consumption of caffeine doses greater than 1 g is consistent with signs of toxicities, and doses ranging from 5–10 g are potentially fatal. Adverse effects associated with caffeine ingestion include restlessness, nervousness, excitement, insomnia, muscle twitching, and, less frequently, tachycardia and cardiac arrhythmias.[16, 17]

Other Components

Chromium picolinate, a trace element involved in glucose regulation and lipid metabolism, is contained in numerous dietary supplements that claim to increase lean body mass, reduce obesity, and improve lipid profiles. Chromium picolinate sensitizes insulin-sensitive glucoreceptors in the CNS, resulting in appetite suppression, thermogenesis, and downregulation of insulin secretion.[18] This element is generally well tolerated when taken in recommended amounts (50–200 µg/day). The most common adverse effects reported with chromium picolinate are nausea, diarrhea, and constipation.[19] More serious adverse effects include hemolysis, acute liver and renal failure, and episodes of cognitive and perceptual changes.[20, 21]

Hydroxycitrate, a natural fruit acid of the genus *Garcinia*, is often used in Indian cuisine and is promoted as an appetite suppressant. Inhibition of hepatic citrate lyase by hydroxycitrate decreases production of malonyl-CoA in hepatocytes. This action inhibits fatty acid oxidation and stimulation of gluconeogenesis.[22] The most common adverse effects associated with hydroxycitrate are diarrhea, nausea, and vomiting. Central nervous system stimulation has not been reported.[23]

L-Carnitine, a carrier molecule responsible for the transport of long-chain fatty acids across the mitochondrial membrane, is required for energy metabolism. After transport, fatty acids are used primarily by skeletal and cardiac muscles for oxidation and subsequent energy production. This effect has led to the addition of L-carnitine to many dietary supplements. L-Carnitine is associated with transient nausea, vomiting, and gastritis; however, CNS stimulation has not been reported.[24]

Willow bark extract, a precursor to aspirin, has been used for centuries as an effective antiinflammatory and analgesic agent. Willow bark inhibits cyclooxygenase enzymes involved in prostaglandin synthesis. Similarities in mechanism of action and potential toxicities (including gastrointestinal upset, ulceration, and bleeding) of willow bark and aspirin resulted in the FDA's classifying willow bark as potentially unsafe; CNS stimulation, however, has not been reported.[25, 26]

Conclusion

This case report describes an episode of seizure-like activity in a previously healthy, young man after several weeks of Hydroxycut consumption. Daily intake of ma huang (ephedra) by this patient was 60 mg, which exceeds the FDA's proposed maximum for daily consumption of ephedra alkaloids (24 mg). In addition, the patient's intake of caffeine was more than 600 mg/day. The combination of ephedra alkaloids and caffeine in Hydroxycut may have resulted in a synergistic effect, contributing to sympathomimetic toxicities. The product does not comply with the FDA's 1997 or most recent proposed regulations for ephedra alkaloids.

The Naranjo score,[27] which assesses the causality of drug-related adverse events, in this patient was 6, indicative of a probable ADR (Table 2). Although many case reports describe cardiovascular and nervous system effects of products containing ephedra alkaloids, this is the first case report of seizure due to Hydroxycut. This case report supports the need for regulation of products containing ephedra alkaloids. Due to the increase in demand and the lack of regulation of herbal products, it is imperative that health care providers actively question and educate patients about the use of herbal products. All suspected ADRs resulting from alternative medicine or dietary supplements, regardless of causality, should be reported to the FDA's MedWatch program or to the Special Nutritionals Adverse Event Monitoring System (SN/AEMS), an FDA database of adverse events associated with "use of a special nutritional product: dietary supplements, infant formulas, and medical foods."[3] With more knowledge of postmarketing adverse effects, health care providers can inform consumers and make recommendations more accurately than before about the safety of herbal products.

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