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Legally Lethal Kratom: A Herbal Supplement with Overdose Potential

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ABSTRACT

This case report describes an overdose on kratom, and elicits the potential dangers of overdose on the regulated dietary supplement. A young male presented to the emergency department intubated after being found unresponsive. He was found by his family to be unarousable and agonal breathing with minimal response to naloxone administered by Emergency Medical Services (EMS). Urine toxicology and blood alcohol content were negative. Physical exam was significant for tachycardia, hypotension, and pinpoint pupils with sluggish reactivity to light. Laboratory studies were significant for elevated liver enzymes, blood urea nitrogen, creatinine, lipase, amylase, troponins, and lactic acid. Family members revealed that the patient consumed kratom, which he obtained through an e-commerce business, and had consumed over 500 grams the previous day. Urine sample for kratom on day 3 tested positive with levels of more than 500 ng/dL. The patient received supportive care and, by day 10, pupillary reflexes returned to normal and he was extubated by day 14. Most of the medications/drugs labelled under herbal supplements by the U.S. Food and Drug Administration (FDA) are not regulated and can be purchased over the counter. The safety and side-effect profile of kratom is not well-studied, especially in an overdose scenario.

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KEYWORDS
Food and Drug Administration; herbal dietary supplement; kratom; overdose

Kratom is a widely available, unscheduled herbal supplement that has been used for its opioid-like side-effects. Kratom is derived from an evergreen tree that is indigenous to Southeast Asia; its active ingredients are opioid receptor agonists and it has been used for pain management, traditional medicine, self-treatment of withdrawal from prescription opioids, and recreational uses. Kratom is consumed in the form of pills, resins, concoction, leaf extracts, and leaf powders, amongst others (Brown, Lund, and Murch 2017). It was traditionally consumed in Southeast Asia to aid in manual labor, as its consumption is known to increase the ability to perform this labor. In the last decade or so, kratom has made its way into Europe and the United States (US), and has seen an increased consumption. It was unregulated until 2016, available over the counter and freely on the Internet. Over the last few years, there has been international recognition of kratom and increased concerns about its abuse potential. Recently, there have been regulations put in place governing the manufacturing, distribution, and selling of kratom as a dietary supplement. Although minor side-effects of kratom have been described, management in an overdose scenario has not been described in the medical literature to the best of our knowledge. Here, we describe the clinical features and laboratory findings of a young man who presented to the hospital with a kratom overdose.

Case presentation

A 36-year-old male Caucasian manual laborer presented to the emergency room intubated by Emergency Medical Services (EMS). The patient was found unresponsive at home by his family for an unknown period of time. Naloxone was administered by the EMS for possible opioid overdose. In the emergency room, examination was significant for Glasgow Coma Scale (GCS) of 3; pupils were found to be pinpoint and not reactive to light and cool peripheries. Vital signs were significant for heart rate (HR) of 130, blood pressure (BP) 80/40 millimeters of mercury, temperature 36.8°C, partial pressure of oxygen (PaO2) of 200 on mechanical ventilator support, with fraction of inspired oxygen (FiO2) of 80%.

Laboratory tests showed significant increased serum aspartate aminotransferase (AST) of 1347 U/L, alanine amino transaminase (ALT) of 3717 U/L, hyperkalemia,

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acute kidney injury, increased serum anion gap of 18, lactic acid of 7.1 mmol/L, and creatinine kinase of 700 U/L. Urine and blood toxicology screens were negative. Computed tomography (CT) of the abdomen and pelvis revealed cholestasis without cholecystitis. CT of the chest was normal. Acute Physiology and Chronic Health Evaluation (APACHE) III prognostic system score was calculated to be 95, indicating high in-hospital mortality.

Our patient was hemodynamically stabilized with fluid resuscitation and intravenous norepinephrine. Meningoencephalitis was ruled out with a lumbar puncture and seizures with continuous video electroencephalogram (VEEG). No obvious source of infection was identified. Further questioning of the patient's family revealed that he had been consuming a green-colored herbal supplement to increase his stamina for the past few weeks with increasing daily dosage. The green powder was brought to us in a clear plastic bag and a thorough Internet study was done to compare the clinical features and laboratory findings with the physical characteristics of the powder. It was soon discovered that kratom might be one of the possibilities. A urine sample was tested for kratom, which returned positive for 7-hydroxymitragynine level more than 500 ng/ml, indicating overdose. He was conservatively managed in the intensive care unit and, over the next week, his pupillary reflexes returned to normal. Patient's neurological examination, vital signs and the abnormal laboratory values also normalized. He was extubated by the end of week two, and was ultimately discharged to an acute rehabilitation institute for physical therapy.

Discussion

The genus *Mitragyna* is an evergreen tree that is native to Southeast Asia and Africa. The products of the tree have been consumed by local populations for generations for ethnomedical uses in the treatment of mild pain and also as a mild anxiolytic (Brown, Lund, and Murch 2017; Adkins, Boyer, and McCurdy 2011). The products of the tree are known to have opioid-like sedating properties at high doses and amphetamine-like stimulating properties at lower doses. Kratom effects vary widely, depending on the strain of the plant, with strains like the red vein variety from Bali being more of a pain reliever, while the white or green vein varieties from Malaysia exhibit stimulating properties (Warner, Kaufman, and Grundmann 2016). The first case of kratom withdrawal was described in 1957. In the last few decades, kratom has made its way into Europe and the U.S., and an estimated 40 million people use kratom for treatment of chronic pain and treating opioid withdrawal symptoms. Thus far, there have been no kratom overdose cases reported from Southeast Asia, most likely due to the low-dose chronic use of the supplement, which in turn increases the overdose threshold.

Over 25 alkaloids have been isolated from this plant. Depending on the origin of the plant and the type of derivative, kratom is also known to have stimulating properties and hence is used by manual workers to aid with stamina, as with our patient. Part of kratom's spectrum of uses is its aid in withdrawal from opioid usage (Boyer et al. 2008). The active ingredients is theorized to act on serotonin and adrenergic pathways, and can explain its array of uses, but experimental proof has been obtained only for its action on mu, kappa, and delta opioid receptors (Philipp et al. 2009). Its action on alpha-2 adrenergic agonistic activity may explain its use in treatment for opioid withdrawal, much like clonidine (Philipp et al. 2009). The main metabolite of kratom, mitragynine, follows linear pharmacokinetics with a two-compartment model. Most of the main active metabolites are metabolized through the liver and only a minor amount through the urine, making its detection possible, although it is not part of routine urine toxicology screening (Philipp et al. 2009; Trakulsrichai et al. 2015). Hematological and clinical chemistry parameters did not alter in chronic kratom users according to one cross-sectional study (Singh et al. 2017), but we suspect that the abnormalities in liver function tests and laboratory values in our patient were due to acute heavy use. Urine kratom levels are not routinely tested, making it practically impossible to diagnose without a high suspicion.

Treatment of kratom overdose is supportive in nature, and no antidotes have been tested thus far. Response to naloxone is partial at best. Kratom is currently classified as a "drug and chemical of concern," but is not in the Controlled Substance Act of the Drug Enforcement Administration (DEA). There is an increasing awareness of its abuse potential within the U.S. DEA and Food and Drug Administration (FDA) officials are taking small but definitive actions to limit its distribution and sales, removing it from the list of consumable herbal supplements. There is no federally mandated ban on kratom, but it is controlled by a number of states to limit its sale and consumption (DEA 2017). Currently, it is deemed a "plant supplement not for consumption." We hope with this article may highlight the importance of identification of lesser-known supplements with abuse potential.

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