CASE REPORT

Cardiac arrest in a young healthy male patient secondary to kratom ingestion: is this 'legal high' substance more dangerous than initially thought ?

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Accepted 5 July 2019

To cite: Abdullah HMA, Haq I, Lamfers R. *BMJ Case Rep* 2019;**12**:e229778. doi:10.1136/bcr-2019-229778

SUMMARY

Kratom is a psychoactive herb that has stimulant properties at low doses and has opioid-like properties at higher doses. It has been used for centuries in southeast Asia as a stimulant but has gained increasing popularity as a substitute for opioids in western countries as it is easily available. As most cases of kratom use involve other drugs too, the Food and Drug Administration (FDA) has stopped short of restricting kratom due to difficulty in assessing the adverse effects of kratom alone. We present the case of a young healthy 35-year-old man who suffered a cardiac arrest due to kratom use with no other coingestants. He was subsequently intubated and found to have systolic dysfunction and small brain infarcts. Fortunately, he made a successful recovery and was discharged after a stay at thebehavioural health centre. Our case highlights the potential adverse effects of kratom and the need to regulate its use.

BACKGROUND

Kratom is a psychoactive herb, belonging to the Rubiaceae family. It has been used for centuries in southeast Asia, mostly as a stimulant by workers to increase their stamina, but increasingly by teenagers too. Other uses include treatment of pain, cough, diarrhoea and use for opioid withdrawal.[1] It is used in many forms, most commonly as chewable leaves and also boiled to make tea. More recently, it has been available as a powder, or in capsule form too, especially in western countries.[2] At higher doses, it acts as an opioid, acting on the mu and delta receptors. It can cause similar effects as an opioid, also results in withdrawal symptoms and neonatal abstinence syndrome.[3]

Though it has been relatively well-tolerated by communities in southeast Asia who take it in low doses for chronic durations, there have been increasing reports of serious adverse events over the last decade or so. These range from mild withdrawal symptoms and endocrine abnormalities to more serious effects including seizures, posterior reversible encephalopathy syndrome (PRES), hepatotoxicity, cardiotoxicity

and even death.[4–9]

The FDA issued an initial warning in November 2017 about the dangers of using kratom and later attributed 44 deaths in the USA to this agent.[10] Similar warnings were also issued by Canada. They stopped short of regulating kratom, primarily because of the difficulty in assessing the adverse effects of kratom alone, as most cases of kratom abuse involve multiple coingestants. This has also led to a serious discussion among medical professionals and researchers about the need for regulation of this agent.

Our case was significant in the sense that there was no other associated drug ingestion.

CASE PRESENTATION

A 35-year-old man with a significant past history of substance abuse, currently on parole, was found unresponsive and not breathing by his co-residents at his residence. emergency medical services (EMS) found him pulseless and administered cardiopulmonary resuscitation (CPR). Return of spontaneous circulation was achieved after 2 cycles of CPR and epinephrine. He was intubated in the field and brought to the hospital. The only other pertinent history prior to the patient's arrival at the hospital was that the patient had a large quantity of kratom in the form of powder on him when he was seen by EMS and the police. He had a past medical history of polysubstance abuse. These included alcohol abuse, prescription medication use including benzodiazepines and opioid pain medications, marijuana and methamphetamine (street name - crystal meth). However, he had been through incarceration and rehabilitation

and denied using any illicit substances recently.

At presentation, the patient was intubated and could not provide any history. His physical examination revealed a temperature of 95.4°F, pulse of 72, BP of 98/77 mm Hg and respiratory rate (RR) of 18. The patient appeared pale with cold-clammy extremities. He was saturating 100% at FiO2 of 40%. Neurological examination revealed a glascow coma scale (GCS) of 3/15, bilateral pinpoint pupils that were not reactive, and clonus present in both the lower extremities. The cardiovascular, gastrointestinal and respiratory examination was otherwise unremarkable.

INVESTIGATIONS

Laboratory tests done on presentation showed a potassium of 5.9 mmol/L, pH of 7.17, with an anion gap of 30, HCO3 of 19 mmol/L, serum creatinine of 3.0 mg/dL from a baseline of 0.6, aspartate transaminase (AST) of 282 IU/l, alanine transaminase (ALT) of 273 IU/l, creatinine kinase (CK) of 4000 U/L and

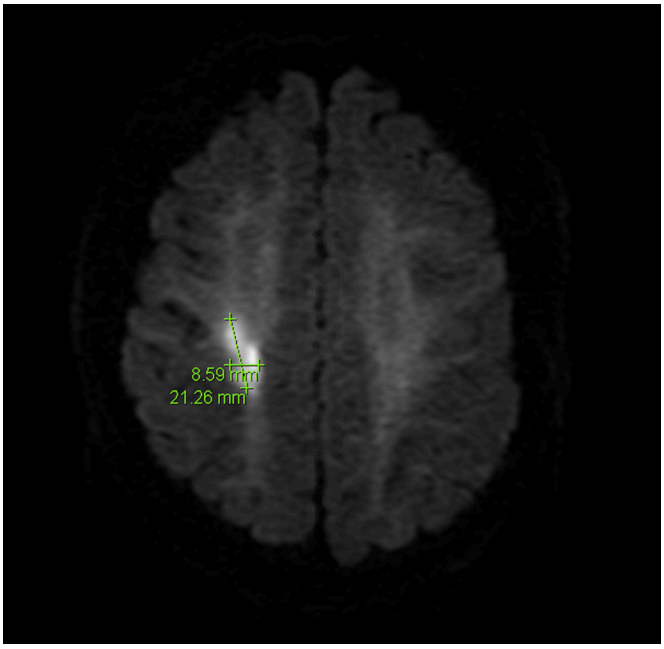

Figure 1 An MRI done after the hypothermia protocol showed scattered foci of infarcts in the B/L hemisphere in a watershed distribution, with the largest infarct measuring 2.1×0.9 cm in the right corona radiate.

troponin I of 0.37 μ/L. Besides these, the complete blood count (CBC), complete metabolic panel (CMP) and clotting profiles were otherwise unremarkable. A CT head, without contrast, at presentation was unremarkable. The patient also had an echo on admission due to elevated troponin I, that revealed left ventricular systolic dysfunction with a left ventricular ejection fraction of just 20% from a normal baseline, probably due to his recent cardiac arrest. A urine drug screen at admission was negative for any drugs. At admission, the patient also had some tonic–clonic movement; however, a continuous electroencephalogram (EEG) ruled out any seizure activity.

DIFFERENTIAL DIAGNOSIS

The patient at presentation was thought to have overdosed with some substance, but his drug screen was negative, and blood alcohol levels were normal. However, the EMS and police reported they had found a large amount of kratom on the patient. After extubation, the patient did admit to using kratom for his opoid dependence. He obtained a large quantity of kratom in the form of powder from a local Vape store. The powder was used to make a tea and he drank it numerous times a day.

TREATMENT

The patient was initially admitted to the intensive care unit , with the neurocritical and internal medicine teams managing the patient. He was put on hypothermia protocol and subsequently rewarmed over the 48 hours. Over these 48 hours, the patient's hypotension, shock, acute kidney injury, acidosis/lactic acidosis and rhabdomyolysis resolved. Troponin I and liver function tests (LFTs) also trended down over the next few days. An MRI done after the hypothermia protocol showed a scattered foci of infarcts in the B/L hemisphere in a watershed distribution, with the largest infarct measuring 2.1×0.9 cm in the right corona radiate (figure 1). These were thought to be secondary to hypoxic brain injury, but the overall volume of the infarct was small. The patient was thought to have some degree of anoxic brain injury. However, over the next 48 hours after rewarming, sedation was titrated down, the patient eventually woke up, was following commands and was subsequently extubated.

After extubation, the patient continued to show some signs and symptoms of opioid withdrawal, including severe anxiety, nausea, tremors, sweating and dilated pupils. He was closely monitored for this and managed symptomatically. This resolved by day 8. The patient also had a repeat echocardiogram, that showed a normal left ventricular systolic function. In the meantime, the patient was able to walk again after physical therapy for a few days.

OUTCOME AND FOLLOW-UP

The patient was seen by our mental health/chemical dependency team. He did try to drink a sanitizer fluid once during his hospital stay due to his severe craving for opioids. He was discharged to an inpatient behavioural health facility for the management of his substance abuse and was subsequently discharged back to the halfway house where he was brought from. He was scheduled for a regular follow-up with the behavioural health centre who started the patient on suboxone for his opioid dependence.

DISCUSSION

Kratom is a psychoactive herbal compound derived from the mitragyna speciose tree. It has been used for centuries by communities in southeast Asia as a stimulant. However, at higher doses, it has opioid-like properties and is increasingly being used a substitute for opioids or for dependence on opioids, especially in western countries.[1–3] Kratom has become increasingly popular in the USA. The exact prevalence of its usage is not known. However, it was estimated in 2016 that several million consumers were buying it from across an estimated 10 000 retail locations all around the USA. It also has an estimated market of 207 million dollars.[11]

Almost 20 different alkaloids have been isolated from kratom. The most abundant and extensively studied alkaloid is mitragynine. Mitragynine is thought to be the producer of most of the psychoactive effects of kratom.[3 12] It acts as an agonist at the mu and kappa receptors but as an antagonist at the delta receptor, which may explain the lesser frequency of respiratory depression associated with kratom.[3 13 14] Kratom works as a stimulant at lower doses (up to 5 g of raw leaves), and has opioid-like properties at higher doses (>5 g of raw leaves).[13] Most authors classify kratom as an opioid, based on the fact that it has similar invivo effects, causes physical dependence similar to that of opioids, has known cross-tolerance to opioids, is chemically similar to opioids and has an affinity to opioid receptors.[15] Besides the opioid-like effect through its activity on the mu receptor, kratom has some other effects too, including activation of noradrenergic and serotonergic pathways in the spinal cord, stimulation of postsynaptic alpha adrenergic receptors and blocking the stimulation of the 5-hydroxytryptamine receptor; it also inhibits prostaglandin synthesis. However, the significance of all these effects is not fully known.[3] The chronic use of kratom, like other opioids, does cause dependence and causes opioid-like withdrawal symptoms in such patients, which at times can be severe.[3 16] Some studies have shown a high rate of dependency and withdrawal symptoms among chronic users. One study showed that more than half of the patients who took kratom regularly for 6 months or more, developed severe withdrawal symptoms at cessation.[17 18] In our case, it was more likely that the opioid-like properties of kratom led to respiratory depression and cardiac arrest which can be

Table 1 This table depicts the reported complications from kratom use.[8 19–25 28 35–42]

System affected	Effects/complications
Central nervous system	► Seizures ► Anxiety ► PRES ► Psychosis ► Coma ► Neonatal withdrawal syndromes
Cardiovascular	► Cardiac arrest ► QT prolongation
Endocrine	► Hypothyroidism ► Hyperprolactinemia ► Hypogonadism
Gastrointestinal	► Hepatic cholestasis ► Hepatitis ► Hepatomegaly
Respiratory	► Respiratory arrest

explained by the mechanism of action of kratom as discussed above. It is unlikely to be the result of an idiosyncratic reaction, brought on by a massive overdose and an inherent vulnerability of this particular patient, as these kinds of allergic reactions have not been reported previously with kratom. Also, our patient did not have any dermatologic or laboratory findings that could hint towards an allergic reaction rather than an overdose.[3]

Kratom use at lower doses causes stimulant-like effects, such as anxiety, irritability, and aggression. At higher doses, opioid-like effects including sedation, somnolence, nausea, vomiting, weight loss, dry mouth, itching and constipation have been reported.[3] Serious adverse effects such as seizures, hepatotoxicity and cardiac arrest have also been reported (table 1). Seizures have been increasingly reported with kratom use, especially at higher doses. This has been reported both in combination with other drugs and as a single agent.[3 7 13 19 20] One case reported structural brain lesions in the form of hyperintensities in the globus pallidus, subthalamic nucleus and cerebral peduncles, causing seizures in a young patient with chronic kratom use.[6] It has also been associated with hepatotoxicity in the form of hepatitis, hepatic cholestasis and hepatomegaly.[8 21–24] Most serious of all, kratom has also been associated with cardiac arrest. One mechanism is thought to be QT prolongation.[9 25] In our case, the cardiac arrest was likely from respiratory depression.

There is no standard of care for the treatment of kratom use or overdose. However, chronic users have been successfully treated with buprenorphine-naloxone.[26 27]

Though kratom has been used in the USA for a while, it came into spotlight in 2016 when the Drug Enforcement Agency banned it, but then had to backtrack due to public backlash. In 2018, the Food and Drug Administration reported the number of kratom associated deaths between 2011 and 2017 at 44.[7 10 28 29] There is an ongoing discussion about the need for regulating the use of kratom in the USA and other western countries. However, detractors state that there is still no solid evidence that kratom is harmful because of the difficulty in assessing the adverse effects of kratom alone, as most cases involve multiple coingestants. Also, there have been studies which show that chronic low-dose ingestion has been tolerated by populations in southeast Asia.[30] Detractors also claim that any restriction would affect research into its safety and efficacy, and also restrict research into its potential use for opioid dependence.[31] However, there are increasing reports of people who have been harmed, such as our patient. As such, it is very difficult to ignore these reports and potential side effects. Our patient is a good case study on the harmful effects of kratom ingestion even when it is ingested alone. Considering these potential risks associated with kratom use, it is reasonable to advocate some level of restriction in the availability of kratom.[32] Some states in the USA have already moved to restrict the use and sale of kratom, and it is currently illegal to use or sell kratom in Alabama, Arkansas, Indiana, Tennessee, Vermont and Wisconsin.[33] This does not mean it cannot be studied in the future for the potential treatment of opioid dependence.

An important teaching point is to keep kratom overdose in mind as one of the differentials in cases of suspected opioid overdose when the drug screen is negative. Kratom use poses a unique healthcare challenge as many of the healthcare providers are not even aware of its existence. There have been attempts to make laboratory assays, to help law enforcement and other professionals in detecting kratom use.[34]

Patient's perspective

I was unaware of these side-effects of kratom. In my opinion, this is even more dangerous than the previous opioids I used to take as I was unable to gauge if I was beginning to have overdose symptoms or not. People should be made aware of the side-effects of kratom and what it can really do.

Learning points

- Kratom is a psychoactive herb that has stimulant properties at low doses and has opioid-like properties at higher doses.
- It has been used for centuries in southeast Asia as a stimulant but has gained increasing popularity as a substitute for opioids in western countries as it is easily available.
- As most cases of kratom use involve other drugs too, the Food and Drug Administration has stopped short of restricting kratom due to difficulty in assessing the adverse effects of kratom alone
  - However, there have been increasing reports of serious adverse events over the last decade or soKeep kratom overdose in mind as one of the differentials in cases of suspected drug overdose when the drug screen is negative, especially in patients with presentations suspicious for opioid overdose

Contributors HMAA and IH were involved in writing the manuscript. RL was involved in critically reviewing, proofreading and making corrections to the manuscript. All the authors were involved in the care of the patient.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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