

Kratom Associated Withdrawal Symptoms and Naltrexone: A Case Report

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Abstract Kratom (*Mitragyna speciosa* Korth), an indigenous herb of Southeast Asia, is popularly used to treat withdrawal symptoms associated with opiate addiction and a myriad of ailments including chronic pain, anxiety and hypertension. Its use has significantly increased in western countries because of its widespread advertisement on the internet as a safe, nonaddictive alternative treatment of pain and opioid dependent disorders. This report describes the first emergency case of toxic encephalopathy, rhabdomyolysis, and liver injury in relation to kratom withdrawal syndrome induced by naltrexone in a 49-year old male. The symptoms were resolved with a regimen of dexmedetomidine, lorazepam, oral lactulose, and a bicarbonate drip. Outpatient treatment with lorazepam and tramadol was recommended for further withdrawal symptoms.

Keywords: kratom, withdrawal, opioid, toxicity, naltrexone

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1. Introduction

Kratom is a herbal supplement derived from the Southeast Asian plant known as, *Mitragyna speciosa*. [1] It was used in the past by laborers for its stimulant-like effects at low dosages and opioid-like effects at higher dosages. [2] In the United States, kratom is an unregulated substance that has become popular for recreational use and mitigating opioid withdrawal symptoms. [3] Literature exists supporting kratom's utility in preventing withdrawal symptoms, however, with excessive use it too can lead to dependency and withdrawal. [1]

Kratom can act as an anti-inflammatory and has parasympathetic blocking effects. [4] Though the exact mechanism remains unclear, these effects are attenuated with the administration of naloxone. [4] This suggests kratom's effects are at least partially mediated by opioid agonists. [4,5]

Kratom's heightened popularity has been coupled with increasing abuse. According to the Center for Disease Control, between July 2016 and December 2017, kratom was detected on toxicology reports of 152 unintentional overdoses. [6] Kratom was commonly used with fentanyl (65.1%), heroin (32.9%), benzodiazepines (22.4%), prescription opioids (19.7%), and cocaine (18.4%). [6] Despite the usage of varying substances, coroners deemed kratom the cause of death in 91 of 152 cases. [7] With rising abuse, new research has emerged focusing on the

withdrawal symptoms associated with kratom tapering and abstinence.

To date, no comprehensive studies have investigated kratom withdrawal in its entirety. However, several case reports have documented the presenting symptoms. Cessation of kratom has led to severe muscle spasms, myalgia, chronic pain, seizures, insomnia, and intense cravings. [4,8,9,10,11] Treatment for withdrawal seizures and chronic pain has been successful with buprenorphine. [10,11] In two case reports, withdrawal symptoms were successfully treated with clonidine and hydroxyzine. [8,9]

2. Case

A 49-year-old man with hypertension, anxiety, and depression presented to the emergency department with what appeared to be opioid withdrawal symptoms. He was experiencing tremulousness, agitation, diffuse myalgias, diaphoresis, dyspnea, and muscle spasms. His vital signs were unremarkable. The patient admitted to extensive kratom usage for 3-4 years and, before admission, had attempted to taper off kratom with naltrexone (50 mg) under the guidance of his psychiatrist. His symptoms began abruptly that morning after taking 10 g of kratom followed by a double dose of his prescribed 50 mg of naltrexone (100 mg in total). He also admitted alcohol usage 1-2 times a week. On presentation, the urine drug screen was negative for amphetamines, opiates,

barbiturates, cannabinoids, and cocaine. It was positive for benzodiazepines and tricyclic antidepressants which he took as prescribed by his psychiatrist. His outpatient medication regimen was doxepin 10 mg, testosterone cypionate 200 mg/mL, tamsulosin 0.4 mg, sildenafil 50 mg, naltrexone 50 mg, armodafinil 250 mg, alprazolam 1 mg, clonidine 0.1 mg, and venlafaxine 150 mg.

The patient's symptoms progressed despite management with fluids, lorazepam, ketorolac and ondansetron. He was eventually admitted to the ICU for continued agitation and distress despite repeated attempts at sedation. Overnight he was placed on bipap for acute respiratory failure. His care team witnessed an acute change in mental status, a rapid decline in his oxygen saturation and an apneic episode. Upon further questioning, it was revealed that the patient had previous apneic spells and planned on having a polysomnography evaluation for sleep apnea. His electrocardiogram came back unremarkable with a QT interval of 411 milliseconds; he had a white blood cell count of 15,000 and an elevated total creatine kinase (4687 U/L) indicating acute rhabdomyolysis. He had two troponin levels ≤ 10 ng/L. Computed tomography scan of the head showed no abnormalities. Sepsis workup for his leukocytosis was negative.

On day 2, the patient was treated with IV dexmedetomidine and lorazepam for kratom withdrawal. He also received ketorolac as needed. His symptoms persisted but became milder with time. His creatinine kinase was persistently elevated, and he was started on a bicarbonate drip for his presumed rhabdomyolysis. The patient developed an AST of 112 U/L and an ammonia level of 40 $\mu\text{mol/L}$ at this time. He was started on oral lactulose to resolve his hyperammonemia. An ultrasound of the liver was unremarkable.

On day 4, the patient's AST level returned to 32 U/L. His creatine kinase decreased to 480 U/L. His remaining symptoms included diffuse myalgias, diaphoresis, and mild agitation.

On day 5, he was discharged. He was told to take ketorolac and lorazepam as needed for further withdrawal symptoms.

It was concluded that his clinical course was due to acute toxic encephalopathy secondary to naltrexone-induced kratom withdrawal with complications of rhabdomyolysis and liver injury. The pulmonology consultant attributed his acute respiratory failure to the combined effects of respiratory depression secondary to sedative administration and probable underlying sleep apnea.

3. Discussion

This report details the case of a 49-year-old male with a past medical history of chronic kratom use. He presented to the emergency department in severe opioid withdrawal after ingesting 10g of kratom and 100 mg of naltrexone. The naltrexone was prescribed to him by his psychiatrist to taper down his kratom usage. Upon evaluation in the emergency department, he was found to have electrolyte abnormalities, leukocytosis without fever and elevated CK

levels consistent with acute rhabdomyolysis. Empiric management with fluids, lorazepam, ketorolac, clonidine and ondansetron were unsuccessful. He was admitted to the ICU and placed on a dexmedetomidine lorazepam infusion. The ICU course was complicated by respiratory distress, altered mental status, transaminitis, hyperammonemia, as well as persistent leukocytosis and CK elevation. All imaging studies were unremarkable. His status improved by day 3 of admission with the regimen of dexmedetomidine, lorazepam, oral lactulose, and a bicarbonate drip. He was discharged on day 5 with resolution of rhabdomyolysis, normalization of liver enzymes and adequate mentation. His clinical course was attributed to acute toxic encephalopathy secondary to naltrexone-induced kratom withdrawal syndrome. He was instructed to manage further withdrawal symptoms outpatient with oral lorazepam and Tramadol as needed.

3.1. Kratom Withdrawal Symptoms (KAWS)

Currently, there are several reported cases of Kratom Associated Withdrawal Symptoms (KAWS). The most common presentation is similar to that of mild opioid withdrawal including diaphoresis, rhinorrhea, myalgias, nausea, diarrhea, abdominal pain, piloerection, anxiety and irritability. [12] Symptom onset is typically 12-24 hours after last reported use. [12] The duration of Kratom use prior to the KAWS episode ranged from 1-3 years with doses between 14 to 42 grams daily. [3]

The majority of reported cases of KAWS in literature describe the clinical course of patients who requested inpatient assistance in detoxification from kratom after failed attempts at discontinuation. There are only a few reports available detailing a withdrawal syndrome that required emergency services. One case involved a 43-year-old man admitted for evaluation of a generalized tonic-clonic seizure and signs of opioid withdrawal after abruptly discontinuing his 3.5-year kratom use. [13] He also endorsed co-ingestion with modafinil making the etiology of the seizure episode difficult to discern. [13] Another case describes a 29-year-old male presenting with bilateral arm pain and symptoms consistent with a mild opioid withdrawal syndrome 6 hours after his last dose of kratom. [14] However, the severity of his presentation and need for emergency services was due to the development of thrombophlebitis secondary to intravenous kratom injections. [14]

Presently, there are no reported cases of toxic encephalopathy, rhabdomyolysis, and liver injury in relation to kratom withdrawal syndrome. In fact, the above complications have been documented as rare features of a kratom toxidrome. [15] In addition, there are no available reports cataloging the consequences of kratom usage in conjunction with naltrexone, nor management of this unique clinical situation.

This case provides evidence that a severe sequence of events can occur in the setting of kratom withdrawal including dehydration, altered mentation secondary to toxic encephalopathy, rhabdomyolysis requiring close monitoring of kidney function and liver injury with subsequent elevations in ammonia.

3.2. KAWS Management in the Setting of Naltrexone

This case presents the unusual clinical scenario of kratom withdrawal syndrome in the setting of naltrexone use. This patient developed abrupt and severe withdrawal symptoms when he took 100 mg of naltrexone following 10 g of kratom.

Naltrexone has been documented as a treatment option for those who have already detoxified from kratom and are motivated to continue abstinence. [3] However, there are no cases describing its use in assisting gradual kratom tapering or the consequences of relapsing while naltrexone is active in the body. The situation described in this case shows that kratom withdrawal induced by naltrexone closely parallels that of its ingestion in opioid dependent individuals.

Ingestion of naltrexone in opioid dependent people results in the acute blockade of opioid receptors. [16] This precipitates a severe withdrawal reaction that appears in as little as 5 minutes and lasts up to 48 hours. [16] Symptoms include confusion, agitation, hallucinations, sweating, tachycardia, abdominal pain, profuse vomiting, and diarrhea. [16]

The current standard of management is largely supportive and includes benzodiazepines, antiemetics (eg. metoclopramide), IV fluids, non-opioid analgesics, and antispasmodics (eg. hyoscine). [16] Opioid analgesia is avoided in this clinical scenario because excessive doses are required to compete with naltrexone at receptor sites. [16] Therefore, the large dose needed for symptomatic relief can result in severe side effects such as prolonged respiratory depression. [16]

In this case report, empiric treatment with a regimen similar to the above did not provide symptomatic relief to the patient. He continued to have severe agitation despite repeated attempts at sedation. This problem has not been reported in kratom withdrawal.

The management of kratom withdrawal in the setting of active naltrexone in the body presents a complicated clinical dilemma as opioid analgesics are commonly used in withdrawal cases to avoid the effects of abrupt drug cessation. Management of KAWS in this setting is analogous to that of naltrexone-induced withdrawal in opioid dependent patients. This case provides evidence that a trial of dexmedetomidine can be used if symptoms are refractory to the aforementioned empiric treatment.

In regard to outpatient management of chronic kratom use, it can be reasonably concluded from the consequences of the kratom/naltrexone co-ingestion that initiation of naltrexone in this population should be treated with the same caution used in opioid dependent patients: opioid free for 7-10 days and a supervised naloxone challenge before initiation. [16]

3.3. Kratom Toxidrome

In recent literature, there has been an increase in the incidence of kratom toxicity cases. Although it has been regarded as a “safer” alternative to opioid analgesics, the United States Drug Enforcement Agency cites kratom as having potential for addiction, adulteration, and tolerance. [17] This results in subsequent dose increases and higher

concentrations of the drug needed to achieve the original intended effects. When this is paired with the ease of obtaining kratom, the risk of toxicity becomes substantial.

Severe cases of withdrawal are rarely documented, however there are several cases of kratom toxicity that resulted in life-threatening symptoms. Reported adverse effects include hypothyroidism, hypogonadism, hepatitis, ARDS, posterior reversible encephalopathy syndrome, seizure, and coma. [3] Infrequent but other serious toxicity cases reported intrahepatic cholestasis, a hepatocellular pattern of liver injury, arrhythmias, stress cardiomyopathy and rhabdomyolysis. [15,18,19] The patient in this case had features resembling the rare complications of kratom toxicity including rhabdomyolysis, liver injury and encephalopathy.

Kratom-related deaths are rare but have been reported. Most of these cases involve co-ingestion with another drug. [6] These include: modafinil, carisoprodol, fentanyl, tramadol, diphenhydramine, caffeine, morphine, loperamide, zopiclone, citalopram, lamotrigine, venlafaxine and mirtazapine. [6,20] Of note, kratom overuse is often seen in individuals with comorbid illicit substance use and/or psychiatric conditions. [6,20] Certain cases of death related to kratom involve several medications that are used therapeutically by that population. [20] The patient in this case was taking modafinil and venlafaxine in addition to his chronic kratom ingestion. Therefore, further investigation of its drug-drug interactions, particularly its serotonergic properties, is needed for improved management and potential avoidance of future cases of kratom-related deaths.

4. Limitations

The limitations noted in this case study include an unclear history of kratom usage. We know the duration of use and the amount the patient took the day of presentation, but there is no documentation of his historical use habits before attempting to taper. This produces issues when attempting to correlate the severity of the withdrawal syndrome to the dose/length of time the individual was on the drug. In addition, the mechanism of his rhabdomyolysis, liver injury and acute encephalopathy could only be inferred as directly related to his withdrawal due to the timing and lack of history, symptoms and labs identifying another source. Minimal literature on KAWS and the seemingly contradictory information of these complications appearing in kratom toxicity cases makes the exact causation unclear.

5. Conclusion

Kratom is widely available to the public and its usage is not currently regulated. While it has been regarded as a safer alternative to opioid analgesics, the increasing number of cases documenting adverse health effects related to its overuse should raise concern over the ease of obtainability. Reports such as this highlight the dangerous consequences of not only overdose but withdrawal from the herb as well. Kratom has the potential to precipitate a withdrawal syndrome with life-threatening symptoms

when taken in conjunction with naltrexone. This report also emphasizes the importance of informing healthcare providers on the signs and symptoms of kratom toxicity and withdrawal, its empiric management, treatment alternatives, and rare complications that could arise. Currently there are no clinical trials investigating the proper management of kratom withdrawal and toxicity. Treatment modalities are anecdotal and analogous to opioid dependency management. Further studies evaluating management options as well as the correlation between the length/dose of kratom use and the severity of its withdrawal syndrome are needed to better equip providers with improved knowledge on how to approach these patients in the inpatient and outpatient setting.

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