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Kratom-induced transaminitis with subsequent precipitated opioid withdrawal following naltrexone

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Abstract

Kratom is an herbal supplement that has gained popularity for recreational use within the United States. Kratom exerts opioid-like effects and, although not US FDA approved, is commonly used for self-treatment of pain, withdrawal management from opioids, and euphoria. Drug-related hepatic injury has been associated with kratom use. All of this raises concern for patient safety and monitoring. The potential for additive liver toxicity must be considered when kratom is used concurrently with hepatotoxic, over-the-counter, herbal, and prescription medications. This case report describes a case of kratom-induced liver inflammation complicated by opioid withdrawal that was precipitated by initiation of IM naltrexone. To our knowledge, there are no published case reports related to opioid withdrawal following naltrexone administration in patients using kratom (without other opioids). The purpose of this case report is to demonstrate potential complications that may arise with kratom use and considerations that should be taken prior to initiation of naltrexone in kratom users.

Keywords: kratom, *Mitragyna speciosa*, mirtragynine, liver, transaminitis, naltrexone, Vivitrol

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Background

Mitragyna speciosa, known as kratom, is a tree native to Southeast Asia, belonging to the same family as the coffee plant, *Rubiaceae*. Kratom contains more than 40 indole alkaloids with mitragynine existing as its primary alkaloid constituent.[1] Kratom has been reportedly used as an opium substitute in Malaysia.[2] Kratom leaves are typically smoked, ingested raw, or steeped in tea preparations although other formulations for consumption are also available, such as capsules, tablets, powder, and concentrated extracts.[1]

Kratom use in the United States has become more widespread over the past two decades for self-treatment of pain; mental health conditions, such as depression; and withdrawal from opioids.[3,4] Notably, morphine and kratom share similar opioid-related properties, such as high and selective opioid receptor affinity, competitive interaction with the opioid receptor antagonism of naloxone, and analgesic two-way cross-tolerance.[5] Kratom constituents mitragynine and 7-hydroxymitragynine exert agonistic activity at the μ-opioid receptor, possessing the potential to induce dose-dependent analgesic and euphoric effects.[6] Additionally, kratom possesses activity at many nonopioid central nervous system receptors, including the α-2 adrenergic, adenosine A2a, dopamine D2, and serotonin receptors (5-HT2C and 5-HT7), although currently there is limited data regarding physiological significance and binding affinities to these

receptors.[6] Inhibitory effects on serotonergic 5-HT2A receptors, along with postsynaptic α-2 adrenergic receptor activation, are believed to cause stimulating effects following kratom use.[7-9] Its dopaminergic effects have not been well characterized; however, research suggests mitragynine may have functional antagonistic effects at D2 receptors.[5,10] The aforementioned receptor activities of kratom are summarized in Table 1.

Naltrexone is a high-binding-affinity opioid antagonist that produces its antagonistic effects by competitively displacing opioid molecules at the μ-opioid receptor. Naltrexone is US FDA approved for the treatment of AUD and OUD.[11] Naltrexone has been associated with hepatotoxicity.[11]

Recreational use of kratom has been associated with rare instances of acute liver injury.[12-16] We report a case of kratom-induced liver inflammation complicated by opioid withdrawal symptoms precipitated by initiation of IM naltrexone.

Case Report

A 38-year-old white male with a past psychiatric history significant for stimulant use disorder, OUD, AUD, and PTSD was admitted to a residential rehabilitation treatment program after a 5-day admission to the acute psychiatric unit. While admitted to the acute psychiatric unit, he was started on chlordiazepoxide for alcohol withdrawal and buprenorphine/naloxone for OUD. Upon presentation, his urine drug screen was positive for buprenorphine and benzodiazepines, consistent with inpatient medications. Prior to admission, he had a long-standing history of kratom use in the form of herbal teas; he viewed kratom similar to "green tea or chamomile tea." During admission, the patient requested to discontinue buprenorphine/naloxone and expressed interest in transitioning to IM naltrexone injection. At that time, he denied use of kratom or any other substances with opioid properties. For confirmation of kratom use, his urine sample was sent to test for mitragynine (kratom) on day 10 of admission.

The treatment team planned to initiate IM naltrexone for comorbid AUD and OUD pending his mitragynine urine toxicology result. On day 23, the mitragynine urine test came back positive despite his denial of kratom use. Initiation of naltrexone was deferred due to potential risk of opioid withdrawal precipitation. A second mitragynine urine test was sent on day 24. Subsequently, the patient disclosed to his psychiatrist that he had been ordering kratom via a food delivery service to the residential treatment facility. The patient reported that his last kratom use was on day 29 when he drank 3 large teas of kratom. On day 31, his comprehensive metabolic panel showed significantly elevated AST of 173 U/L and ALT of 586 U/L, 4 and 10 times the upper limit of normal, respectively. Due to significant AST/ALT elevations, naltrexone initiation was again deferred. The second mitragynine level remained pending and, therefore, was not used to guide naltrexone administration given the 2-week latency for results. On day 33, his liver function tests (LFTs) remained elevated, and his IM naltrexone injection was again deferred due to abnormal labs. As a result of continued LFT elevations, a third mitragynine urine screen was collected. For exclusion of other origins of elevated LFTs, hepatitis A, B, and C screenings were found to be negative for active infection and acetaminophen concentration was found to be within normal limits. Additionally, albumin, bilirubin, and alkaline phosphatase remained within normal limits throughout admission. During this time, there were no pertinent medication changes that would impact LFTs.

On day 45, the patient elected to receive his first dose of naltrexone as his LFTs were now less than 10 times the upper limit of normal. Per patient report, this was 16 days after his last kratom use. At that time, the third and most recent mitragynine screen remained pending. On day 46, he reported gastrointestinal symptoms, including nausea, vomiting, and abdominal pain as well as muscle spasms, "uncontrollable limb jerking," and yawning, which he believed was an adverse reaction to the injection. On day 47, the patient presented to the facility's emergency department with primary complaint of dehydration, vomiting, and diarrhea. He received 1 dose of ondansetron and IV fluids and was then discharged back to the residential treatment program. Symptoms resolved within 72 hours after naltrexone injection. He stated that he believed he was "allergic to the shot" although, given a long history of documented substance use while admitted to residential treatment programs, his previous positive mitragynine results, and hallmark withdrawal symptoms, his clinical team suspected his reaction was likely precipitated by opioid withdrawal. Routine, biweekly urine drug screens were negative for all other opioids throughout admission. On day 47, a fourth and final mitragynine drug test was collected and sent.

TABLE 1: Mechanism of action of kratom receptor activity[5,6,8-10]

Receptors	Proposed Activity
μ-Opioid receptor	Agonist
α-2 Adrenergic receptor	Agonist
Adenosine A2a receptor	Agonist
Dopamine D2 receptor	Antagonist
Serotonin 5-HT2C and 5-HT7 receptors	Antagonist

TABLE 2: Treatment course throughout admission to residential rehabilitation treatment program

Days From Admission	AST (U/L)	ALT (U/L)	Mitragynine	Comments
Baseline	16	13		One week prior to admission
Day 10			Urine specimen #1 collected	
Day 23			Results #1: Positive	
Day 24			Urine specimen #2 collected	
Day 29				Reports last kratom use
Day 31	173	586		
Day 32	161	520		
Day 33	130	462		
Day 35			Results #2: Positive	
Day 36			Urine specimen #3 collected	
Day 39	136	350		
Day 45				Naltrexone IM injection administered
Day 47	59	181	Urine specimen #4 collected	Went to the emergency department for dehydration, vomiting, and diarrhea
Day 49			Results #3: Positive	
Day 51				Discharged
Day 60			Results #4: Positive	

On day 49, his third mitragynine urine drug test returned positive. The patient elected to discharge early on day 51 as he felt he no longer benefitted from the treatment program. On day 60, 9 days after he was discharged, his fourth and final mitragynine urine drug test returned positive indicating potential continued use throughout his course of admission (see Table 2).

Discussion

Kratom is currently not approved by the FDA due to the lack of safety and efficacy for treatment of any condition in addition to concerns for risk of addiction, abuse, and dependence. Furthermore, the Centers for Disease Control and Prevention find that kratom exposure–related calls to poison centers increased tenfold from 26 in 2010 to 263 in 2015.[17] Kratom is associated with serious adverse effects, such as respiratory depression, hallucinations, delusions, aggression, vomiting, seizures, withdrawal effects, and death.[18-21] Animal studies in mice exposed to kratom reveal observations of liver toxicity characterized by elevated triglycerides, cholesterol, AST, ALT, and albumin; anemia; and histological evidence for hepatic cellular damage following acute or subchronic exposure to kratom.[21-23] Kratom is also associated with instances of acute liver injury in previous case reports.[12-15] In this case, other potential causes of transaminitis were ruled out based on lab work. Naltrexone is also associated with transaminitis, but hepatic enzyme abnormalities were present in this patient prior to the administration of IM naltrexone. As such, it was determined that naltrexone as a possible cause would be considered doubtful as indicated by the Naranjo adverse reaction probability scale (score of 0), and kratom would be considered probable based on the Naranjo scale (score of 6). Due to the patient electing to discharge early, we were unable to collect any additional LFTs after day 47 of admission. The patient was admitted to the hospital several months later with similar lab findings (AST/ALT elevated, all other labs within normal limits). The patient was reporting continued kratom use at that time as well but was no longer prescribed naltrexone.

Prior to this psychiatric admission, the patient had previous trials of both oral and IM naltrexone without tolerability issues. A test dose with naloxone or naltrexone was not completed because the veteran reported his last use of kratom and opioids was greater than 2 weeks prior. Given that the veteran did not develop opioid withdrawal during his 5-day course of buprenorphine in the acute psychiatric unit, it is likely that the veteran was not taking kratom prior to inpatient psychiatric admission. Following his positive mitragynine confirmatory results and onset of opioid withdrawal, it was discovered that the patient misrepresented his kratom use. Subsequently, the patient disclosed to the medical team that he was ordering kratom via food delivery services to the residential setting. This case emphasizes the importance of screening and counseling on herbal supplement use and its potential to

cause opioid-like dependence prior to initiation of naltrexone. It also supports that a test dose of either oral naltrexone or injectable naloxone should be considered prior to initiating IM naltrexone given that substances such as mitragynine and fentanyl derivatives may not show on most routine urine drug screens. In addition, a naloxone or naltrexone test dose should be recommended prior to starting IM naltrexone in all patients, including patients who report abstinence from opioids and kratom. A MEDLINE search revealed no published case reports of precipitated kratom withdrawal following naltrexone administration.

In this case, we regularly tested for kratom throughout admission. Testing was completed using liquid chromatography–mass spectrometry, which can provide definitive, qualitative results, but there is a 14-day latency between collection of specimen and results. Throughout the admission, we were able to determine that mitragynine remained detectable in his urine. Quantitative rather than qualitative testing was not available at our facility but would have been preferred to monitor trending of mitragynine levels.

Mitragynine is predominantly metabolized by the liver and exhibits linear kinetics with a long elimination half-life of around 24 hours. This is reported by a clinical study[24] that examined its pharmacokinetics in chronic users who consumed kratom leaves estimated at 6 to 24 mg mitragynine per dose. Based on this information, it can be predicted to take nearly 5 days to fully clear kratom tea from the body. Studies are limited regarding elimination half-life of alternative dosage forms or unregulated marketed products; thus, pharmacokinetics may vary. In addition, kratom is found to be detectable in urine for up to 2 weeks after last use.[12] These variables in pharmacokinetics and urine testing present barriers to initiation of opioid antagonist treatment and place patients with AUD and OUD at risk of withdrawal when starting treatment. To avoid such complications, clinicians may consider naloxone or oral naltrexone challenge prior to initiating long-acting injectable naltrexone or utilization of buprenorphine/naloxone for kratom maintenance and withdrawal.[25,26]

Conclusion

Despite their poorly understood safety profiles, herbal supplements, such as kratom, are gaining in popularity. Previous case reports establish that kratom use is associated with hepatoxicity. This case report provides evidence that chronic, heavy use of kratom creates physiological opioid dependency placing AUD and OUD patients at risk of precipitated withdrawal when starting naltrexone.

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