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Precipitated withdrawal with kratom use following naltrexone administration

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Abstract

Kratom is an herbal supplement with reports of use for natural pain relief or treatment of opioid withdrawal symptoms. Kratom has metabolites that bind to and agonize mu-opioid receptors similar to opiate medications. There have been reports of serious adverse reactions, with a potential for dependence with long-term use and withdrawal that may occur upon discontinuation. Naltrexone can result in abrupt withdrawal symptoms when used with opioids or opioid-like supplements such as kratom. This case report describes withdrawal precipitated by naltrexone administration in a patient with undisclosed chronic kratom use. This case highlights the importance of thorough assessment of all self-administered herbal and over-the-counter supplements as they may have serious interactions with other prescribed medications and affect therapeutic outcomes.

Keywords: kratom, mitragyna, naltrexone, withdrawal

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Background

Kratom (*Mitragyna speciosa*) is an herbal supplement derived from a tree native to Southeast Asia and is used for pain, depression, anxiety, and opioid withdrawal treatment.[1] Kratom leaves can be crushed and smoked, chewed raw, or steeped in tea, but recently have been supplied commercially as bulk powders, capsules, tablets, and concentrated extracts.[1] Several different alkaloid components are found in kratom; however, mitragynine and 7-hydroxymitragynine are believed to be the active constituents.[1] Mitragynine is a partial mu-opioid receptor agonist that is 25% more potent than morphine, while 7-hydroxymitragynine is a mu-opioid agonist estimated to be 10 times as potent as morphine.[1,2] Additional non-opioid receptor activity of kratom includes dose-dependent antagonism at dopamine (D_2) and serotonin receptors ($5\text{-}HT_{2C}$ and $5\text{-}HT_7$), as well as agonism at postsynaptic alpha (α-2) receptors.[3,4] Kratom's mu-opioid agonist activity provides analgesic and euphoric effects to individuals and may lead to misuse.[2] Additional effects at dopamine, serotonin, and alpha receptors can also result in stimulatory effects of kratom use, including hallucinations, aggression, and delirium.[5] Reports of seizures, liver damage, respiratory depression, severe withdrawal, and even death have also been associated with kratom consumption.[6-8] The FDA have made several statements warning against the use of kratom.[9] In 2014, the FDA identified kratom as an unapproved drug because of their concern of effects similar to opioids that may expose users to the risks of misuse and addiction.[10]

Naltrexone acts as a competitive antagonist at opioid receptor sites.[11] Its oral and extended-release injectable formulations are FDA approved for opioid use disorder because of its high affinity for mu-opioid receptors and for alcohol use disorder via modification and increase of the hypothalamic-pituitary-adrenal axis activity.[12] Similarly, recent studies have evaluated

an off-label use of oral naltrexone for weight loss, alone or in combination with bupropion, via regulation of food intake by appetite suppression and reduction of emotional eating.[13]

Patients initiated on naltrexone should be opioid free for a minimum of 7 to 10 days to avoid risk of precipitated opioid withdrawal.[11] Given opposing effects at the mu-opioid receptor, withdrawal symptoms from kratom have been reported when used in combination with naltrexone.[8] The risk of withdrawal is increased because of the lack of patient education and counseling upon sale of kratom, as well as increased availability without a prescription.[14]

Case Report

A 56-year-old white male with a past medical history of hypertension, dyslipidemia, obstructive sleep apnea, vitamin D deficiency, obesity (BMI = 39 kg/m^2), and anxiety presented to a community hospital emergency department with a chief complaint of a perceived acute medication reaction to naltrexone. The patient reported he was newly prescribed naltrexone 50 mg once daily for weight loss and took the first dose before arrival to the emergency room. Before admission, the patient was also taking amlodipine and metoprolol. He states that within 30 minutes of taking naltrexone, he became restless, felt cold and sweaty, and had an increased heart rate. Diphenhydramine, 25 mg, was self-administered before ER arrival without improvement. The patient denied any history of drug or alcohol misuse. His urine toxicology was negative for all substances, including methadone, fentanyl, and buprenorphine (Table). Ethanol concentration was minimally elevated at 10.9 ng/mL (normal <10 ng/mL), which he reported was owing to drinking occasionally (2-3 beers) on the weekends.

Within 2 hours of arrival in the emergency room, the patient became increasingly agitated, experiencing visual hallucinations. His hallucinations caused him to be confused, altered, and aggressive toward staff members. His comprehensive metabolic panel, ammonia level, and urine analysis were all unremarkable. A head CT showed no acute abnormalities. Because of the severity of his agitation, the patient was given 7.5 mg olanzapine intramuscularly, 4 mg midazolam intravenously, and 1 mg lorazepam intravenously, with minimal improvement (Figure). The patient and his wife continued to deny alcohol or opioid misuse; however, the patient scored a 39 on the Clinical Institute Withdrawal Assessment–Alcohol Scale Revised (CIWA-AR) and had symptoms similar to delirium tremens, including confusion, hallucinations, and hypertension.[15] The initiation of dexmedetomidine infusion was required, and he was placed on institution driven CIWA protocol as the etiology of his agitation was still unknown at that time. He required admission to the ICU for acute agitation, hyperactive delirium, and altered mental status.

TABLE: Toxicology report obtained on admission to the emergency room

Toxicology	Level (Normal)
Blood	
Ethanol	10.9 mg/dL (<10 mg/dL)
Acetaminophen	<10 mcg/mL (10-30 mcg/mL)
Salicylate	<10 mg/dL (0-30 mg/dL)
Urine	
Amphetamines	Not detected
Methadone	Not detected
Fentanyl	Not detected
Buprenorphine	Not detected
Barbiturate	Not detected
Benzodiazepine	Not detected
Cannabinoids	Not detected
Cocaine	Not detected
Opiates	Not detected

The neurology service was consulted for the possibility of posterior reversible encephalopathy syndrome because of the patient's unexplained agitation with altered mental status and hypertension. During a medication history obtained by the clinical pharmacist and neurologist, the patient's wife reported the patient's use of large amounts of kratom powder, which he ingests every morning with his coffee for knee pain. This information was not previously disclosed before neurology consultation. The confirmation of kratom use and a Naranjo score of 8 suggested a probable adverse drug reaction of kratom withdrawal from naltrexone use. Once his altered mental status and agitation resolved, the patient confirmed he purchased kratom powder, called "maeng da kratom" (green vein *Mitragyna speciosa*), from a local smoke shop. He stated that he mixed high doses equivalent to 1 tablespoon (8 g) in his coffee every morning.

Kratom withdrawal was managed with an α-2 agonist, dexmedetomidine, and on-demand intravenous lorazepam. Because of the severity of his symptoms and unknown ingestion of kratom, this patient required maximum doses (1.2 mg/kg/h) of dexmedetomidine and received 24 mg lorazepam within the first 24 hours of ICU admission per CIWA protocol. The patient's withdrawal symptoms lasted about 36 hours, and he was able to be discharged home directly from the ICU after 48 hours. He was extensively counseled by the pharmacist on the side effects of kratom and the interaction of kratom with naltrexone. During a follow-up phone call discussion after discharge, the patient reported discontinuation of both kratom and naltrexone. He stated that his primary care physician prescribed opioids for knee pain in replace of kratom, and he is now apprehensive to try new weight loss medications after this experience.

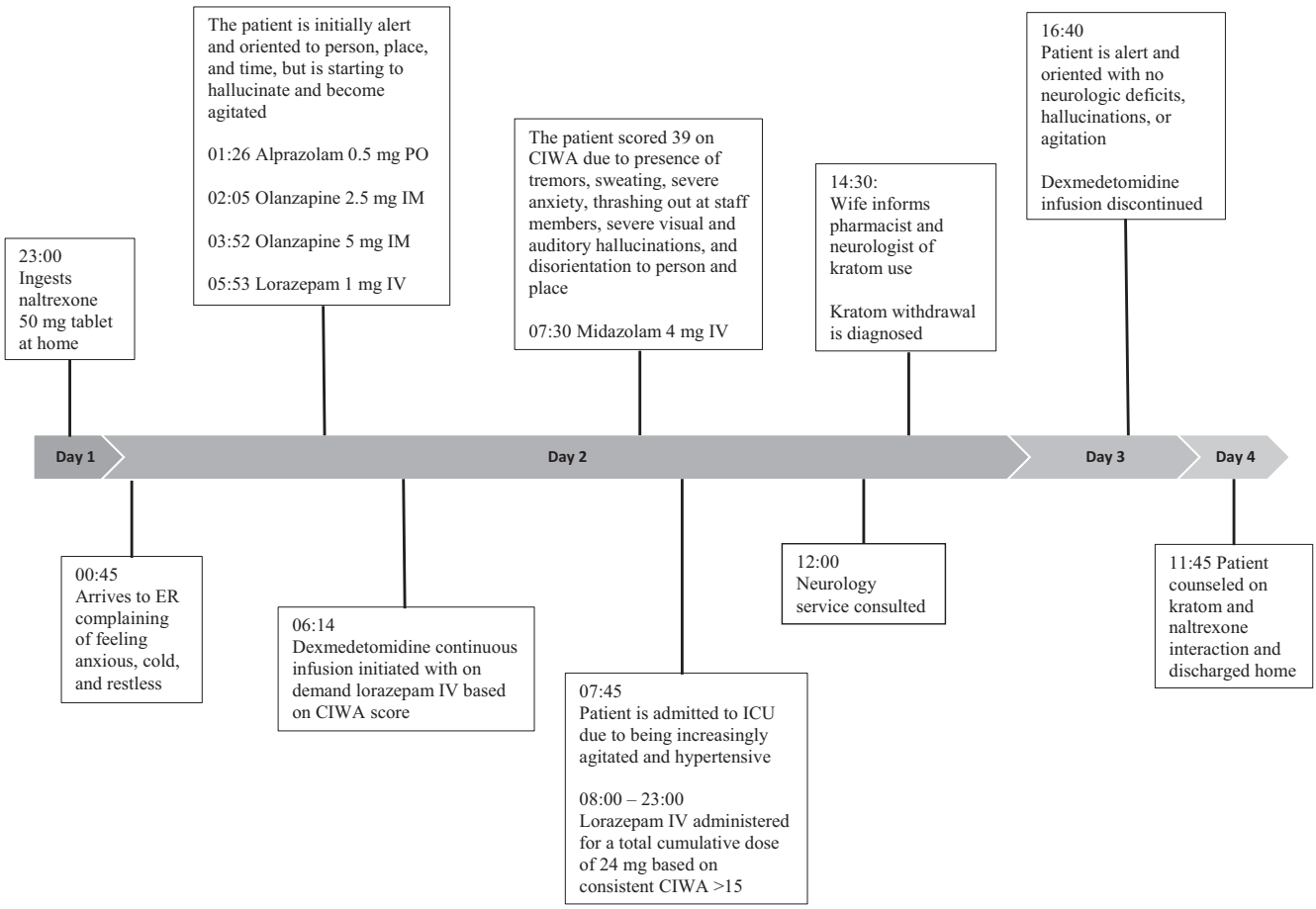

FIGURE: Timeline of ingestion, symptoms, and treatment

Discussion

Kratom is a readily available herbal supplement that can be easily purchased by individuals at gas stations, herbal shops, and via the internet. The FDA issued its first official warning against consumption of kratom in 2014.[2] In 2016, the drug enforcement agency attempted to place kratom and its active constituents of mitragynine and 7-hydroxymitragynine as a Schedule 1 under the Controlled Substance Act; however, the proposal was withdrawn after strong opposition from kratom support groups.[2] Within the United States, kratom is currently illegal in 6 states (Alabama, Arkansas, Indiana, Rhode Island, Vermont, and Wisconsin), and legislation is pending to ban sales in several other states.[9] Doses recommended by facilities that sell kratom differ based on dosage form but widely range from 1 to 8 g per day.[3]

This case is unique in that naltrexone was used for an off-label use of weight loss. It is more common for naltrexone to be prescribed for FDA-approved indications including opioid and alcohol use disorders. Oral naltrexone has a short half-life of 4 hours as well as complete absorption with a serum time to peak of about 60 minutes.[11]

Kratom is not well known or understood by many prescribers. Kratom may interact with CYP1A2, CYP2C19, CYP2D6, and CYP3A4 substrates by potentially increasing concentrations and clinical effects of drugs metabolized by these enzymes.[4] Animal research shows low absorption of mitragynine with oral bioavailability of only 3.03%.[16] Mitragynine is metabolized by the liver and has a half-life of about 24 hours.[17,18] As a result, it is believed that it will take approximately 5 days for kratom to be cleared by the body. Fortunately, oral naltrexone's short time to peak absorption and half-life resulted in this patient's withdrawal symptoms lasting approximately 36 hours. This case shows the importance of screening and counseling patients on the use of herbal supplements and the potential interactions with prescribed medications.

There have been other case reports of precipitated kratom withdrawal with naltrexone use.[8] The novelty of this case is that it describes a situation where naltrexone was used for an off-label indication for weight loss in an individual without a substance use disorder who was consuming high doses of kratom daily. These cases may signify potential changes to common practice. Considerations include using a naltrexone test dose within an appropriate health care

setting or potential integration of appropriate screening on herbal supplement use, by including mitragynine and fentanyl derivatives in common urine drug screens.

Conclusion

The use of herbal supplements, including kratom, may not be benign. In addition, newer research may result in increased use of naltrexone for indications outside of substance use disorders. This case report highlights the potential effects of kratom use, including the risk of precipitated withdrawal when given with interacting pharmacotherapy.

References

1. Jansen KLR, Prast CJ. Ethnopharmacology of kratom and the Mitragyna alkaloids. J Ethnopharmacol. 1988;23(1):115-9. DOI: 10.1016/0378-8741(88)90121-3
2. Griffin OH, Webb ME. The scheduling of kratom and selective use of data. J Psychoactive Drugs. 2018;50(2):114-20. DOI: 10.1080/02791072.2017.1371363. PubMed PMID: 28937941.
3. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology. 2018;134:108-20. DOI: 10.1016/j.neuropharm.2017.08.026. PubMed PMID: 28830758.
4. Obeng S, Kamble SH, Reeves ME, et al. Investigation of the adrenergic and opioid binding affinities, metabolic stability, plasma protein binding properties, and functional effects of selected indole-based kratom alkaloids. J Med Chem. 2020;63(1):433-9. DOI: 10.1021/acs.jmedchem.9b01465
5. Singh D, Müller CP, Vicknasingam BK. Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. Drug Alcohol Depend. 2014;139:132-7. DOI: 10.1016/j.drugalcdep.2014.03.017. PubMed PMID: 24698080.
6. Forrester MB. Kratom exposures reported to Texas poison centers. J Addict Dis. 2013;32(4):396-400. DOI: 10.1080/10550887.2013.854153. PubMed PMID: 24325774.
7. Trakulsrichai S, Tongpo A, Sriapha C, Wongvisawakorn S, Rittilert P, Kaojarern S, et al. Kratom abuse in Ramathibodi poison center, Thailand: a five-year experience. J Psychoactive Drugs. 2013;45(5):404-8. DOI: 10.1080/02791072.2013.844532. PubMed PMID: 24592666.
8. Jensen AN, Truong Q-N, Jameson M, Nadal CN. Kratom-induced transaminitis with subsequent precipitated opioid withdrawal following naltrexone. Ment Health Clin [Internet]. 2021;11(3):220-4. DOI: 10.9740/mhc.2021.05.220. PubMed PMID: 34026398.
9. Kraoma [Internet]. Kratom Legality 2022: Map, Legal Status, and Ban Updates. c2022 [cited 2022 July 15]. Available from: https://kraoma.com/kratom-legality-United-States/
10. US Food and Drug Administration [Internet]. Import alert: Detention without physical examination of unapproved new drugs promoted in the U.S. [cited 2023 Feb 17]. Available from: https://www.accessdata.fda.gov/cms_ia/importalert_190.html
11. DailyMed database [Internet]. Naltrexone tablet, film coated; Accord Healthcare Inc. Bethesda (MD): National Library of Medicine (US); c2017 [cited 2022 June 21]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=49aa3d6d-2270-4615-aafa-b440859ab870
12. Williams KL, Broadbear JH, Woods JH. Noncontingent and response-contingent intravenous ethanol attenuates the effect of naltrexone on hypothalamic-pituitary-adrenal activity in rhesus monkeys. Alcohol Clin Exp Res. 2004;28(4):566-71. DOI: 10.1097/01.alc.0000121655.48922.c4. PubMed PMID: 15100607.
13. Kulak-Bejda A, Bejda G, Waszkiewicz N. Safety and efficacy of naltrexone for weight loss in adult patients—a systematic review. Arch Med Sci. 2021;17(4):940-53. DOI: 10.5114/aoms.2020.96908. PubMed PMID: 34336024; PubMed Central PMCID: PMC8314402.
14. Coe MA, Pillitteri JL, Sembower MA, Gerlach KK, Henningfield JE. Kratom as a substitute for opioids: results from an online survey. Drug Alcohol Depend. 2019;202:24-32. DOI: 10.1016/j.drugalcdep.2019.05.005. PubMed PMID: 31284119.
15. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84(11):1353-7. DOI: 10.1111/j.1360-0443.1989.tb00737.x. PubMed PMID: 2597811.
16. Parthasarathy S, Ramanathan S, Ismail S, Adenan MI, Mansor SM, Murugaiyah V. Determination of mitragynine in plasma with solid-phase extraction and rapid HPLC-UV analysis, and its application to a pharmacokinetic study in rat. Anal Bioanal Chem. 2010 Jul; 397(5):2023-30. DOI: 10.1007/s00216-010-3707-7.
17. Castillo A, Payne JD, Nugent K. Posterior reversible leukoencephalopathy syndrome after kratom ingestion. Proc (Bayl Univ Med Cent). 2017;30(3):355-7. DOI: 10.1080/08998280.2017.11929647. PubMed PMID: 28670086; PubMed Central PMCID: PMC5468044.
18. Wananukul W, Trakulsrichai S, Sathirakul K, Auparakkitanon S, Krongvorakul J, Sueajai J, et al. Pharmacokinetics of mitragynine in man. Drug Des Devel Ther. 2015;9:2421-9. DOI: 10.2147/DDDT.S79658. PubMed PMID: 25995615; PubMed Central PMCID: PMC4425236.