The ToxIC NOSE (Novel Opioid and Stimulant Exposure)

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7-hydroxymitragynine: A High-Risk Supplement Marketed as Kratom

Introduction

Kratom is derived from the *Mitragyna speciosa* tree that is native to Southeast Asia.[1] Mitragynine, the main active substance in kratom, is responsible for its neuropsychiatric effects.[1] This alkaloid interacts with adrenergic, opioid, dopamine, and serotonin receptors to modulate pain, mood, and alertness.[1,2] Due to its complex receptor interactions, individuals utilize kratom at low doses for its stimulant effects, and at higher doses for its sedative and opioid-like effects.[1,2]

7-hydroxymitragynine (also called 7-OH mitragynine) is a more potent semi-synthetic derivative of kratom.[3]

The ToxIC Novel Opioid and Stimulant Exposure (NOSE) Reports

Through the ongoing support of the Opioid Response Network (ORN) since 2020, the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) has implemented an enhanced sentinel detector field within the ToxIC Core Registry to identify novel and emerging opioid and stimulant exposures. Once an emerging trend or risk is identified, ToxIC releases a quarterly report.

The goal of this project is to disseminate this novel information to the medical toxicology community as well as the ORN as part of a Rapid Response program.

For more information on the ToxIC Core Registry and data collection, please visit: www.toxicregistry.org

Although it is not naturally present in the *Mitragyna speciosa* plant, 7-hydroxymitragynine is an artifact of the drying process used in the manufacturing of kratom.[2,3] It is also created through the oxidation of mitragynine via hepatic and intestinal cytochromes.[2] The primary distinction between mitragynine and 7-hydroxymitragynine lies in their opioid receptor activity.[2,3,4] 7-hydroxymitragynine exhibits significantly greater potency at the mu-opioid receptor, with binding affinity estimated to be approximately 10 times that of morphine.[2,3,4] Additionally, it is metabolized to mitragynine pseudoindoxyl, a compound that also demonstrates high potency at mu-opioid receptors and contributes to the overall opioid-like effects.[4]

With the growing popularity of kratom, demand for its production has increased significantly, resulting in a wide range of products containing kratom, 7-hydroxymitragynine, and mitragynine pseudoindoxyl.[3,4] As a result, there is greater potential for unintentional exposure to 7-hydroxymitragynine and mitragynine pseudoindoxyl, which have substantially stronger opioid activity than mitragynine.[3,4] Although 7-hydroxymitragynine and mitragynine pseudoindoxyl are chemically distinct from mitragynine and from each other, they are often sold under the general label of "kratom."[2,3,4] This lack of transparency can mislead consumers, who may be unaware they are ingesting substances with different and potentially more potent clinical effects. The following report presents a case of confirmed 7-hydroxymitragynine toxicity reported to the Toxicology Investigators Consortium (ToxIC) Drug Overdose Toxico-Surveillance (DOTS) Reporting Program.[5]

Case Presentation

A 45-year-old female patient with a past medical history of asthma, attention deficit hyperactivity disorder, depression, and chronic kratom use presented to the emergency department via ambulance after being found unconscious and covered in emesis. No prehospital medications, such as naloxone, were administered.

On arrival, her vital signs were as follows: blood pressure 144/86 mmHg, heart rate 88 bpm, respiratory rate 22 breaths per minute, oxygen saturation 93% on room air, and temperature

36°C. On examination, she exhibited central nervous system (CNS) depression and was noted to be covered in emesis. Initial laboratory testing revealed a glucose level of 118 mg/dL, lactate of 1.3 mmol/L, and creatine phosphokinase of 122 U/L, all within normal limits. A blood gas was not performed. The only medication administered in the emergency department was ondansetron.

After several hours of observation, the patient returned to her baseline mental status and was able to provide additional history. She reported ingesting a white powder labeled as kratom approximately 4 to 6 hours prior to presentation, which she had purchased from a local shop. She stated this was her first time using that particular product but had a history of kratom use spanning the previous seven years. She purchased this product because she thought it would help her relax and feel more “zen” and explicitly denied suicidal intent. She denied use of any other substances aside from sencha shots, a caffeine-containing product.

The patient was discharged home after a period of observation without complication. However, she returned to the emergency department 11 days later in cardiac arrest and subsequently died. No additional information regarding her return visit was available.

A blood sample was obtained and sent to the Center for Forensic Science Research and Education for comprehensive toxicological analysis, which detected the presence of amphetamine, caffeine, yohimbine, mitragynine, and 7-hydroxymitragynine.

Discussion

This case illustrates the potential dangers associated with 7-hydroxymitragynine exposure. While kratom-related toxicity has been reported in the literature, including cases involving coma and respiratory depression requiring naloxone administration, this patient was found to have both mitragynine and 7-hydroxymitragynine in her system. She was found unresponsive with signs of CNS depression, consistent with opioid toxidrome. Given the known pharmacologic activity of 7-hydroxymitragynine and its significantly greater potency at the mu-

opioid receptor compared to mitragynine, it is likely that her symptoms were primarily driven by this compound.[2,3,4]

Interestingly, the patient reported using a new "kratom" product that differed from what she had previously used. Rather than experiencing the expected relaxing effects that she was seeking, she developed signs of acute opioid toxicity. Like traditional opioids such as morphine, fentanyl, oxycodone, and heroin, agonism at the mu-opioid receptor can result in respiratory and CNS depression, respiratory arrest, and death.[1,2,3,4] While we cannot confirm the cause of her subsequent cardiac arrest and death 11 days later due to lack of autopsy data, the role of 7-hydroxymitragynine cannot be excluded.

This case underscores the clinical significance of 7-hydroxymitragynine as a distinct and more potent risk factor compared to mitragynine alone. Unlike mitragynine, 7-hydroxymitragynine can produce opioid-like effects at lower doses, increasing the risk for overdose.[2,3,4] The unregulated nature of kratom products in the United States, which are not approved or regulated by the FDA, means consumers cannot reliably determine the presence or concentration of 7-hydroxymitragynine. This variability poses a significant health risk and may lead to serious outcomes, including coma and death, even in individuals with a history of kratom use.

Conclusion

Although kratom is often used for its stimulant and relaxation effects, there are significant toxicities associated with both kratom and the semi-synthetic 7-hydroxymitragynine byproduct. With increasing kratom use and production, there is growing concern about greater exposures to 7-hydroxymitragynine which as mentioned above, can be produced in the manufacturing of kratom for commercial use as well as from metabolism of kratom in the body. Given that 7-hydroxymitragynine is more potent at the mu-opioid receptors, it is crucial to educate the public on the potentially dangerous side effects.

References

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Help is here! The *Opioid Response Network (ORN)* is your resource for no-cost education, training and consultation to enhance efforts addressing opioid and stimulant use disorders.

ORN has consultants in every state and territory to deploy across prevention, treatment, recovery and harm reduction.

Share your needs via the "Submit a Request" form at www.OpioidResponseNetwork.org. Within one business day, your regional point person will be in touch to learn more.

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