ToxTalks:

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

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7-hydroxymitragynine: The newest smoke shop craze

What is 7-hydroxymitragynine?

7-hydroxy-mitragynine (7-OH-MIT or 7-OH) is a potent indole alkaloid derived from the *Mitragyna speciosa* (kratom) tree. Kratom refers to powdered or extracted leaves from the tree and contains dozens of alkaloids, while 7-OH is a single, naturally occurring alkaloid present in kratom in very small amounts (often <0.05% of leaf dry weight). It acts as a partial agonist at μ-opioid receptors, and as an antagonist at δ- and κ-opioid receptors. When kratom is ingested, a small amount of 7-OH is produced endogenously in humans via CYP3A4-mediated oxidation as an active metabolite of mitragynine. Recently, the 7-OH has been synthetically produced and is now commonly sold in smoke shops.

Image: Wikimedia Commons

Pharmacology

7-OH binds much more strongly to the μ-opioid receptor than mitragynine, ranging from 5-22 times greater depending on the study. In animal models, it produces much more potent pain relief and typical opioid effects such as sedation and euphoria. Functionally, it behaves as a partial agonist at the μ-opioid receptor, producing potent analgesia and sedation but with a ceiling on how much respiratory depression it causes compared to full agonists like morphine.

One unique feature of 7-OH is biased agonism, meaning it activates G-protein signaling at the μ-opioid receptor while only weakly triggering the β-arrestin-2 pathway3. Because β-arrestin-2 signaling is linked to many classic opioid effects including respiratory depression, constipation, and tolerance, some studies suggest that 7-OH may cause fewer of these adverse effects at analgesic doses. However, at high doses or repeated use, it can still produce the full range of opioid toxicities, including respiratory depression.

At other opioid receptors, δ and κ, 7-OH acts as an antagonist. The δ-receptor is normally linked to mood effects

and tolerance. Theoretically, blocking the δ-receptor would blunt tolerance development and reduce some antidepressant or euphoric effects. Conversely, the κ-receptor is typically associated with dysphoria, anxiety, and hallucinations. Antagonism of this receptor may reduce those unpleasant effects and instead enhance reinforcement and euphoria, potentially increasing its liability for abuse.

Increase in Popularity

Although only a very small fraction of mitragynine is metabolized to 7-OH in the body (less than 2% of the administered dose in mice), the metabolite is believed to account for much of kratom's desirable effects due to its high potency. Capitalizing on this, manufacturers have begun producing pure 7-OH directly, most often in the form of chewable tablets, effectively isolating the primary source of euphoria. This has led to its nickname, the "gas station opioid", and it is increasingly sought out for its strong analgesic effects, euphoric profile without dysphoria (unlike some mixed opioids), and easy accessibility.

Image courtesy of Blue Ridge Poison Center

Many users turn to 7-OH as an alternative to traditional opioids as an attempt to self-manage or taper from opioid addition. It is often marketed and perceived as a "natural" and therefore safer substitute for prescription opioids. However, this perception is misleading and dangerous: products sold in smoke shops are entirely unregulated, and concentrated 7-OH is pharmacologically more similar to morphine or fentanyl than to raw kratom leaves.

Clinical Effects and Management

The clinical presentation of 7-OH toxicity closely mirrors opioid intoxication, with findings such as CNS depression, miosis, respiratory depression at high doses, constipation, and pruritis. With very high doses or concentrated products, more severe outcomes including apnea, coma, and death are possible. Because these preparations are typically obtained from smoke shops, they may be adulterated or mixed with other psychoactive substances, which can alter the clinical picture. Management of acute toxicity centers on airway protection and ventilatory support in patients with respiratory depression. 7-OH responds to naloxone, although the effective dose may vary. Initial therapy should begin with standard dosing (0.04-0.4 mg IV), titrated upward as needed to reverse respiratory

depression. 7-OH has a longer half-life than naloxone, so repeat dosing or a continuous naloxone infusion may be required. Patients should be placed on continuous telemetry, end tidal CO2 monitoring, and observed for several hours to ensure that re-sedation does not occur.

Dependence and subsequent withdrawal can occur with regular 7-OH use. Clinical features resemble opioid withdrawal and may include anxiety, myalgias, rhinorrhea, yawning, GI distress, insomnia, and irritability. Given 7-OH's much greater potency at the μ-opioid receptor compared with mitragynine, dependence is more likely to develop with chronic 7-OH use than with kratom leaf products. Management is similar to that of opioid withdrawal with supportive care including hydration, antiemetics, clonidine for autonomic symptoms, loperamide for diarrhea, and NSAIDs for myalgias. For patients with severe or persistent withdrawal, medications for opioid use disorder such as buprenorphine may be appropriate.

Summary

7-OH represents a new but familiar opioid challenge: legally available, widely accessible, and marketed as "natural" yet carrying the same clinical risks as conventional opioids. Clinicians should be aware of this substance and maintain a high index of suspicion, particularly when evaluating patients with unexplained opioid-like toxidromes or who report smoke shop or gas station supplement use.

References available upon request