ToxTalks:

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

In Partnership with the UVA Division of Medical Toxicology – Department of Emergency Medicine

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Kratom

Kratom, derived from the leaves of Migranyan speciosa, a tree native to Southeast Asia, has garnered increasing attention in the United States. An estimated 2.1 million US residents used kratom in 2020. Traditionally, kratom leaves were chewed or brewed into tea to address various ailments, including cough, diarrhea, pain, and opioid withdrawal symptoms. They were also consumed to boost energy and appetite.

There are over 25 active alkaloids in kratom but mitragynine and 7-hydroxymitragynine are believed to be responsible for the majority of kratom's effects. In the plant, 7-hydroxymitragynine is present in much smaller quantities than mitragynine, but is significantly more potent. The full pharmacodynamic and pharmacokinetic mechanism of kratom have yet to be completely understood or characterized. Analgesic effects come from agonism of mu-opioid receptors, however, kratom functions as an antagonist at kappa and delta-opioid receptors. Additionally, mitragynine depresses locomotor activity through presynaptic dopamine interactions, inhibits neurotransmitter release by reversibly blocking neuronal Ca^{2+} channels, stimulates postsynaptic alpha-2 adrenergic receptors, and blocks 5-HT_2 receptors.

The pharmacological effects of kratom are dose-dependent. In low to moderate doses (1 to 5 grams) users report mild stimulant effects. In moderate to high doses (5 to 15 grams) users experience opioid-like effects. High doses (>15 grams) may result in initial effects such as sweating, dizziness, nausea, and dysphoria followed by euphoria and sedation.

Kratom use has been associated with various significant effects including cardiotoxicity, hepatotoxicity, and mortality. It suppresses the human Ether-à-go-go-Related Gene (hERG) channel (potassium efflux blockade) prolonging action potentials, and increasing risk of Torsades de Pointes. Although rare, kratom use has been associated with acute liver injury. Symptoms may include abdominal discomfort, dark urine, itching, and jaundice. The latency period (time from first use to symptom onset) averages around 20.6 days. There have been multiple

Continued next page

reports of deaths among individuals who ingested kratom, often in combination with other substances. In some cases, kratom was the sole agent detected.

Images: Wikimedia Commons

The pharmacokinetics of kratom in humans remain under-researched. Key factors such as metabolic half-life, protein binding properties, elimination rates, and metabolic pathways are not yet fully understood. In vitro studies suggest that kratom alkaloids inhibit major drug-metabolizing enzymes, including cytochrome P450 (CYP) 2D6 and CYP3A4. This inhibition indicates a potential for pharmacokinetic drug interactions when kratom is co-consumed with medications metabolized by these enzymes.

The internet has increased public access to kratom, leading to its use for both recreational and medicinal purposes. It is commonly available as a powder, extract, or e-liquid for vaporizers. However, kratom products are unregulated, resulting in variable formulations and strengths. They may also contain intentional or unintentional contaminants, leading to unpredictable user experiences. Kratom mixed with O-demethyltramadol, an active metabolite of the weak opioid analgesic medication tramadol, is marketed as “krypton” in Germany. Phenylethylamine has been found in kratom products sold in New York State.

Kratom's legal status varies globally. It is banned in certain countries, such as Australia and Thailand. In the United States, kratom is classified as a "drug of concern" by the Drug Enforcement Administration (DEA), and its legality varies by state and locality. Due to growing public health concerns, the U.S. Food and Drug Administration (FDA) issued a warning in November 2017 regarding the risks associated with kratom use. In 2023, Virginia passed the Kratom Consumer Protection Act, limiting the use and sales of kratom to those over the age of 21 and also requiring transparent labeling. Its purported medicinal properties for treating chronic pain and opioid addiction have sparked considerable debate.

Management of kratom intoxication is similar to that of opioid overdoses. Patients should be observed for central nervous system and respiratory depression. Other possible effects include nausea, vomiting, miosis (constricted pupils), and confusion. Hallucinations and psychosis have also been reported. Supportive care remains the primary treatment approach. Benzodiazepines can be administered to manage agitation or psychosis. Naloxone may be used to reverse respiratory depression, though this has not been systemically studied. Standard urine drug screens do not typically detect kratom or its alkaloids. However, testing for mitragynine is available through some reference laboratories. Healthcare practitioners should remain vigilant, as patients may present with atypical symptoms due to unknown contaminants in kratom products. Tolerance and dependance have been described in chronic users and may result in withdrawal. This presents similarly to opioid withdrawal and can likely be treated the same, however clinical data is lacking.

In summary, while kratom has traditional uses and potential medicinal applications, its unregulated status, variable product quality, and potential for adverse effects necessitate caution. Further research is essential to fully understand its pharmacokinetics, safety profile, and therapeutic potential.

For guidance, contact the Blue Ridge Poison Center at 1-800-222-1222 or call the dedicated healthcare provider line at 1-800-451-1428.

#NPPW25

The third week in March is **National Poisoning Prevention Week!** This is an opportunity to remind your patients, clients, and colleagues that anyone is at risk for poisoning, and that poisoning is preventable.

Download our NPPW Toolkit to share prevention messages and other resources. Free.