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Case Report

Two Single-Drug Fatal Intoxications by Mitragynine

George S. Behonick[1,*], Christina Vu[2], Larry Czarnecki[2], Maisie El-Ters[2] and Kevin G. Shanks[1]

[1]Axis Forensic Toxicology, 5780 W. 71st Street, Indianapolis, IN 46268, USA
[2]Coconino County Health and Human Services Medical Examiner's Office, 4402 East Huntington Drive, Flagstaff, AZ 86004, USA
*Author to whom correspondence should be addressed. Email: gbehonick@axisfortox.com

Abstract

Mitragyna speciosa, a species of plant that is native to Thailand, Malaysia and Southeast Asia, contains two major psychoactive alkaloids: mitragynine and 7-hydroxymitragynine. Pharmacologically, the alkaloids exhibit biphasic effects—at low doses, stimulant effects are realized, while high doses exhibit sedative effects. For years, the plant has been used recreationally and medicinally for these effects, but its use has been implicated in and associated with intoxications and deaths. In this case report, we describe two cases whereby decedents presented with single-substance fatal intoxications by mitragynine in the absence of other postmortem toxicological findings. The cases entail young male decedents in outdoor settings (e.g., driving a vehicle and bicycle). Postmortem blood concentrations were 2,325 and 3,809 ng/mL. The medical examiner certified the cause of death as acute mitragynine intoxication in both cases. The toxicology results presented become useful when considering mitragynine to be the offending agent in lethal single-drug intoxications; further, the information included is pertinent to medical examiners, forensic pathologists, forensic toxicologists and emergency department personnel in evaluating possible poisoning and lethality by mitragynine.

Introduction

Mitragyna speciosa, also known as kratom, is a plant native to Thailand, Malaysia and Southeast Asia. The leaves of the plant contain several indole alkaloids, with the two major substances being mitragynine and 7-hydroxymitragynine. The plant itself has been used by people, typically as a chewed leaf or brewed into a tea, but the leaves of the plant can also be pulverized and then smoked or placed into capsules for oral consumption (1, 2). Mitragynine makes up ∼60% of the alkaloid content of the plant, with 7-hydroxymitragynine accounting for ∼2% of the alkaloid content, but this alkaloid content varies according to the strain of kratom being used (3, 4).

These alkaloids exhibit biphasic effects. At low doses, stimulant effects are realized, while high doses exhibit sedative effects. Pharmacologically, mitragynine and 7-hydroxymitragynine demonstrate a high affinity for the *mu* (μ) opioid receptor, with mitragynine being ∼13 times more potent than morphine and 7-hydroxymitragynine being 4 times more potent than mitragynine (3, 5–7). Mitragynine has also been shown to block the stimulation of serotonergic receptors and stimulate adrenergic receptors as well as act as an inhibitor of various cytochrome P450 enzymes including CYP1A2, CYP2D6 and CYP3A4 (8, 9).

The US Federal government does not consider mitragynine or 7-hydroxymitragynine controlled substances, but the Drug Enforcement Administration has classified them as drugs and chemicals of concern (10). The substances are not approved by the Food and Drug Administration for any medical application (11). States have passed various pieces of legislation that may control either the alkaloids or the plant itself (12–14). Kratom has been implicated in or associated with many intoxications and deaths, but its role in the cause of death (COD) is still debated by many forensic professionals (15–27).

The toxicology results presented become useful when considering mitragynine to be the offending agent in lethal single-drug intoxications; further, the information included is pertinent to medical examiners (MEs), forensic pathologists, forensic toxicologists and emergency department personnel in evaluating possible poisoning and lethality by kratom.

Experimental

Specimen collection and testing protocol

During autopsy, the ME collected postmortem iliac blood specimens in polypropylene tubes and bottles that contained sodium fluoride. Urine and vitreous fluid were also collected for both cases. Specimens were sent to the Axis Forensic Toxicology's facility for toxicological analyses.

The analysis of volatiles (acetone, ethanol, isopropanol and methanol) in the blood was completed by headspace gas chromatography with flame ionization detection. A comprehensive blood screen for 350+ substances was completed by liquid chromatography with quadrupole time-of-flight mass spectrometry (LC–qToF-MS). Drug classes included in the LC–qToF-MS testing were amphetamines, analgesics, anesthetics, anticholinergics, anticonvulsants, antidepressants, antidiabetics, antifungals, antihistamines, antipsychotics, barbiturates, benzodiazepines, cannabinoids, cardiovascular agents, gastrointestinal medications, hallucinogens, muscle relaxants, opioids, sedatives/hypnotics, stimulants, urological pharmaceuticals and novel psychoactive substances including substituted cathinones, designer benzodiazepines, fentanyl

analogs and other designer opioids and synthetic cannabinoids. Urine was tested for routine drugs of abuse and prescription medications by a targeted liquid chromatography with triple quadrupole mass spectrometry assay. Vitreous fluid is only analyzed for volatiles if the blood is also positive for volatiles; it was not tested in either of our two cases.

Materials

The reference standard for mitragynine was obtained from Cayman Chemical Company (Ann Arbor, MI, USA) and the reference internal standard for mitragynine-d_3 was purchased from Cerilliant Corporation (Round Rock, TX, USA). Acetone (high performance liquid chromatography (HPLC) grade), acetonitrile (HPLC grade), isopropyl alcohol, (HPLC grade) and methanol (HPLC and American Chemical Society (ACS) grade) were purchased from Fisher Scientific (Pittsburgh, PA, USA). Formic acid (98%) was obtained from Sigma-Aldrich, Inc. (St. Louis, MO, USA). Deionized water from the laboratory's water treatment system (18.2 MΩ/cm) was used.

Organic extraction

The calibration curve (5–1,000 ng/mL), negative quality control specimen, low positive quality control specimen (100 ng/mL), high positive quality control specimen (400 ng/mL) and postmortem blood samples were prepared by a protein precipitation extraction with acetonitrile. A 1-mL aliquot of mitragynine-d_3 internal standard solution in acetonitrile (20 ng/mL) was added to 500 µL of whole blood. The samples were vortex mixed for 5 min and centrifuged at 3,000 RPM for 10 min. A 100-µL aliquot of the organic supernatant was transferred to a new culture tube and evaporated to dryness under nitrogen gas flow. The residue was reconstituted in 200 µL of deionized water and transferred to a plastic autosampler vial.

Instrumental analysis

Instrumental analysis was performed on a Waters Acquity UltraPerformance® Liquid Chromatograph coupled with a Waters Acquity Triple Quadrupole Detector tandem mass spectrometer. The chromatographic separation was completed by injecting 10 µL of sample extract onto a Waters Acquity UPLC® HSS T3 column (2.1×100 mm, 1.8 µm particle size), held at 35°C, using a gradient elution of 0.1% formic acid in deionized water and 0.1% formic acid in acetonitrile. Electrospray ionization (mobile phase A) mass spectrometry was performed in positive ionization (mobile phase B) multiple reaction monitoring mode. Two ion transitions were monitored for mitragynine, while one ion transition was monitored for mitragynine-d_3. The capillary voltage was 0.6 kV. The extractor voltage was 4.1 V. The source and desolvation temperatures were 120°C and 500°C respectively. The total run time was 5 min per specimen. Specific parameters for the chromatographic gradient elution and ion mass transitions are detailed in Tables I and II.

Table I. Gradient Elution for the Liquid Chromatograph

Total time (min)	Flow rate (mL/min)	% A	% B
Initial	0.400	93.0	7.0
3.00	0.400	80.0	20.0
3.25	0.400	80.0	20.0
3.65	0.400	30.0	70.0
3.80	0.400	10.0	90.0
4.70	0.400	10.0	90.0
4.80	0.400	93.0	7.0

A- Mobile phase A; B- Mobile phase B.

Method validation

The analytical method for the detection of mitragynine in whole blood specimens was validated as a quantitative assay according to in-house method validation guidelines. The following attributes were assessed during validation: linearity, including limit of detection, lower limit of quantitation and upper limit of quantitation, imprecision and accuracy, exogenous drug interferences and matrix selectivity. The quantitative assay also included other opioid substances in the scope of analysis such as 6-acetylmorphine, morphine, codeine, hydrocodone, hydromorphone, dihydrocodeine, oxycodone, oxymorphone and loperamide. The method validation results specifically for mitragynine are summarized in Table III. This analytical method is not stereoisomer-specific. 7-hydroxymitragynine was not included in the scope of the analytical method.

Case Histories

Case 1

A 37-year-old male left his workplace at ~5 PM for a bicycle ride. He stopped in a forested area for a cigarette and called a friend. The friend reported normal conversation for about a minute, and then heard what sounded like a collapse, followed by about 10 min of breathing, which then ceased. After being notified by the friend, law enforcement located the decedent several hours later by tracing his cell phone. The decedent was discovered to be in a supine position with a bicycle helmet on, lying on a bed of undisturbed pine needles. A cigarette was near his hand and there was no apparent damage to the bicycle, which was parked against a street sign. The scene was consistent with the sudden collapse of the decedent. Remarkable history for the decedent included remote traumatic brain injury, alcohol abuse with withdrawal seizures disorder and smoking. Follow-up investigation revealed that an unmarked bag of kratom was found at the decedent's residence. The decedent, an avid bicyclist, had taken a 50-mile ride the previous day to being found. He was known to add one spoonful of kratom to a 32-ounce water bottle every morning; however, it was unknown to his

Table II. Ion Mass Transitions

Analyte	Ion transition	Type	Dwell time (ms)	Cone voltage (V)	Collision energy (eV)
Mitragynine	399.3 > 174.1	Quantifying	0.02	40	32
Mitragynine	399.3 > 226.1	Qualifying	0.02	40	22
Mitragynine-d_3	402.3 > 238.1	Internal standard	0.01	45	21

Table III. Method Validation Results

Parameter	Acquired result
Linearity	5–1,000 ng/mL
LOD	5 ng/mL
LLOQ	5 ng/mL
ULOQ	1,000 ng/mL
Coefficient of determination (R^2)	0.9994
Calibration model	Quadratic
Weighting	1/x
Accuracy	
100 ng/mL	
Intrarun	108–114%
Interrun	113%
400 ng/mL	
Intrarun	96–112%
Interrun	105%
Imprecision	
100 ng/mL	
Intrarun	0.7–3.5% CV
Interrun	1.8% CV
400 ng/mL	
Intrarun	6.4–9.4% CV
Interrun	8.1% CV
Exogenous interferences	None detected (317 analytes tested)
Matrix selectivity	
10 ng/mL	
Accuracy	102%
Imprecision	7.1% CV
500 ng/mL	
Accuracy	91%
Imprecision	8.6% CV
800 ng/mL	
Accuracy	92%
Imprecision	6.3% CV

The LOD was administratively defined as the same value as the LOQ; no results are reported to be <5 ng/mL.

friends whether the decedent ingested any kratom prior to embarking on these bicycle rides. Autopsy demonstrated some minor cutaneous abrasions with no internal injuries without evidence of acute seizure. The lungs demonstrated congestion (combined lung weight, 1,030 g); however, other autopsy findings included unremarkable gross and microscopic examination of the other internal organs. Toxicological analyses performed on the postmortem iliac blood revealed mitragynine (2,325 ng/mL) and cotinine (qualitative). The urine drug screen by LC–MS for 28 various prescription and illicit drugs was negative. The ME certified COD as acute mitragynine intoxication and manner of death as accident.

Case 2

According to investigative reports, at ∼7 PM, a 33-year-old previously healthy male was driving his vehicle on a moderately wet four-lane city street when he was witnessed to decrease speed, swerve and crash into a snow embankment at ∼10 mph. Emergency medical services arrived and pronounced him dead at the scene. Evidence of significant trauma was unapparent. The vehicle was undamaged and was not traveling at a high rate of speed. The decedent was following a friend's vehicle back to his residence, which was an ∼5-min drive. The decedent's history was notable for anxiety/depression with a social history of polysubstance abuse (ethanol, cocaine, kratom and marijuana). Inventory of the decedent's personal belongings included a lighter and a generic sandwich size bag, filled ∼1/8 of the way with green powder. Additional investigative information revealed the decedent worked a 12–14-h day, before going to the store that evening. He was accompanied by a friend to the store who stated the decedent appeared to be acting normal with no complaints. The decedent was known to ingest kratom every morning by mixing it with hot water. In previous conversations the decedent stated to friends that it was like drinking a cup of coffee. The decedent purchased kratom from local stores but recently switched to buying it online. Reportedly, a bag of kratom at the decedent's residence contained very little product information. Autopsy revealed a few minor cutaneous abrasions without internal injury. The lungs demonstrated pulmonary edema (combined lung weight, 2,000 g) with microscopic evidence of intra-alveolar edema and smoking type changes without evidence of infection. Toxicological analyses performed on the postmortem iliac blood revealed mitragynine (3,809 ng/mL), cotinine (qualitative) and naloxone (qualitative); the urine drug screen by LC–MS was not remarkable for any positive findings. COD was certified by the ME as acute mitragynine intoxication, with accident as the manner.

Discussion

There have been many mitragynine-related deaths reported in the postmortem toxicology literature over the last decade. Mitragynine may have been a contributing factor to a death classified as an accident with propylhexedrine toxicity as the cause as reported by Holler et al. (15). The ME elected to not include mitragynine toxicity in the COD due to the paucity of drug concentrations in the published literature. Unintentional fatal intoxications with mitragynine and *o*-desmethyltramadol from a herbal blend known as Krypton have been observed. The blood concentrations of mitragynine exhibited a range of 0.02–0.18 μg/g (20–180 ng/g) for nine cases, while measured *o*-desmethyltramadol concentrations in blood ranged 0.4–4.3 μg/g (400–4,300 ng/g). It was believed that the addition of the potent *mu*-receptor agonist *o*-desmethyltramadol to the powder leaves of kratom contributed to the deaths (16). Neerman et al. reported the case of a man who was found unresponsive while in bed and was pronounced deceased at the scene. His postmortem toxicology revealed mitragynine (0.60 mg/L), dextromethorphan (0.28 mg/L), diphenhydramine (0.33 mg/L), temazepam (0.21 mg/L) and 7-aminoclonazepam (0.21 mg/L). The COD was certified as possible kratom toxicity (17). Karinen et al. previously reported a concentration of 1,060 ng/mL in a case of accidental poisoning with mitragynine (18). McIntyre et al. described a kratom-related fatality with mitragynine peripheral blood and central blood concentrations of 230 and 190 ng/mL, respectively. The case included detection of venlafaxine and metabolite, diphenhydramine, mirtazapine and ethanol (19). Bishop–Freeman et al. reported a series of deaths related to the opioid loperamide with three cases involving the detection of mitragynine. The first case involved a man who collapsed while playing basketball. At autopsy, the forensic pathologist observed cardiomegaly. Toxicological analysis revealed mitragynine (<0.05 mg/L), tramadol (<0.25 mg/L) and loperamide (0.24 mg/L). The COD was attributed to loperamide toxicity. The second and third cases involved a married couple who were found deceased in bed together. Various

pills and powders, including kratom capsules, were found at the scene. Toxicological analyses of blood samples from the 33-year-old person revealed mitragynine (0.60 mg/L) and loperamide (0.89 mg/kg). Due to decomposition, blood samples were not able to be taken from the 37-year-old person, but mitragynine was detected in a liver sample (3.5 mg/kg), as well as loperamide (6.5 mg/kg). The CODs in these cases were attributed to both mitragynine and loperamide (20). Domingo et al. published two case reports of deaths attributed to the recreational use of kratom. They concluded that the low mitragynine concentration (10 ng/mL) in one case was at most a contributing factor in the death, while in the second case, a mitragynine concentration (790 ng/mL) was measured in femoral blood alone, was deemed to be an indirect COD as contributing factors to overall sedative effects in the decedent (21). Hughes reported the case of a man found deceased while lying on his bed. Other than intramuscular hemorrhage of the tongue, nothing else remarkable was observed at autopsy. Postmortem toxicology revealed mitragynine (qualitative), quetiapine (12,000 ng/mL) and valproic acid (8.8 μg/mL). The COD was certified as acute toxic effects of quetiapine complicated by mitragynine use (22). Wang and Walker reported a case of multidrug toxicity which primarily implicated mitragynine in an accidental death, believed to be the first reported case of mitragynine-associated fatality in Canada, and at the time believed to be the highest reported blood concentration of 2,500 ng/mL in the medical literature (23). Fogarty et al. reported a series of methoxyacetylfentanyl- and cyclopropylfentanyl-associated deaths. In one of those deaths, mitragynine was also detected in the postmortem iliac blood (890 ng/mL). Other substances present included cyclopropylfentanyl (6.8 ng/mL) and ethanol (0.132%) (24). Matson and Schenk reported the case of a man who was found unresponsive after dinner by a family member and was pronounced deceased at a hospital about 30 min later. During autopsy, left ventricular hypertrophy and pulmonary congestion and edema were observed. Postmortem toxicology was remarkable for mitragynine (1.9 mg/L), delta-9-tetrahydrocannabinol (0.0026 mg/L), caffeine (qualitative), cotinine (qualitative) and naloxone (qualitative). The COD was mitragynine toxicity (25). Gershman et al. reviewed death certificates for the presence of mitragynine and identified 15 related deaths from 1999 to 2017 (26). Four of the 15 deaths were certified as mitragynine toxicity (blood concentrations, 16–170 ng/mL). The authors performed a comprehensive toxicological screening on residual blood samples from three of the four deaths that were ruled as mitragynine toxicity, and other toxicologically relevant drugs such as 5-methoxy-alphamethyltryptamine, etizolam and selegiline were detected. Papsun et al. reported 31 postmortem cases in which mitragynine was detected and included in the COD determination (27). Thirty of 31 cases were certified as multiple drug intoxications, with other central nervous system depressants (benzodiazepines, ethanol and opioids) being present in 28 cases. In one case that was not certified as multiple drug toxicity, the cause was determined to be non-drug related. Mitragynine blood concentrations ranged from 24 to 3,300 ng/mL. In 2017–2018, Mata and Andera detected mitragynine in 20 cases, with blood concentrations ranging from 10 to 4,310 ng/mL (28). In three of the cases, mitragynine was certified as the sole COD—blood concentrations were 1,250–4,310 ng/mL in central blood and 1,590–3,420 ng/mL in peripheral blood. Blood concentrations where mitragynine was ruled as a contributing COD ranged from 10 to 870 ng/mL in central blood and 24.6 to 1,210 ng/mL in peripheral blood.

Kratom is not without risk, but estimates suggest that morphine-like opioids impart a risk of serious toxicity (e.g., overdose), which is thousand times greater than kratom (29). It is acknowledged that users of kratom organically carry other factors that greatly increase the risk of kratom-associated mortality. These factors include concomitant use of opioids, sedatives, alcohol and other drugs as well as coexisting morbidities and disease states that amplify risk. We believe that the two cases reported herein are significant with respect to the measured iliac blood concentrations of mitragynine in view of the broader context of the known decedent histories and circumstances of death. Both decedents were engaged in what otherwise could be considered routine, day-to-day activities. In contrast to many of the aforementioned reports by other investigators, our two cases were remarkable for the absence of any other drugs or alcohol detected in blood together with the opined conclusion by the ME of attributing COD in both cases to acute mitragynine toxicity or intoxication. The mitragynine blood concentrations detected in our two cases (2,825 and 3,809 ng/mL) are consistent with, and in some instances surpass, what has been described in the literature. Clinical effects associated with intoxication by mitragynine include agitation/irritability, tachycardia, nausea, drowsiness/lethargy, vomiting, confusion and hypertension (30). More severe toxicities attributed to this substance included seizure, respiratory depression, bradycardia, cardiopulmonary arrest, asystole, rhabdomyolysis, liver injury and failure and renal failure (31–37).

In conclusion, we report two postmortem cases where the COD was certified as acute mitragynine intoxication. Relative to other literature reports, our cases are unique with respect to identifying mitragynine (via comprehensive toxicology) as the single agent implicated in the COD.

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