Fatal Mitragynine-Associated Toxicity in Canada: A Case Report and Review of the Literature

Carol Wang, Alfredo E. Walker

ABSTRACT

Mitragynine is amongst the more than 40 natural indole alkaloids derived from the *Mitragyna speciosa*, or kratom tree, also referred to as ketum. The compound is unique in that it exhibits dose-dependent clinical outcomes with stimulant effects at lower doses but sedative effects at higher concentrations. It is indigenous to Southeast Asia, where the local population has had extensive experiences utilizing the substance for its medicinal as well as recreational effects. Mitragynine is advertised as an herbal remedy and is readily accessible via the Internet, resulting in its expansive distribution throughout the world. The addictive potential of this substance is quickly becoming recognized and mitragynine has been implicated in multidrug toxicity deaths.

We present a case of the first reported mitragynine-associated fatality in Canada where an independently fatal mitragynine concentration was detected in the postmortem femoral venous blood and the source drug was likely obtained as a powder from Indonesia. *Acad Forensic Pathol. 2018 8(2): 340-346*

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INFORMATION

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INTRODUCTION

Mitragynine is a natural indole alkaloid derived from *Mitragyna speciosa*, or kratom tree (**Image 1**) (1). This tropical plant is indigenous to the Philippine islands, New Guinea, and Southeast Asia including Indonesia, Malaysia, Thailand, and Borneo (1, 2). The alkaloid composition of the kratom plant varies geographically. Indonesian plants consist of higher mitragynine and alkaloid concentrations compared to its southeastern neighbors (1, 3). Mitragynine is among one of the more than 40 psychoactive diastereomers of the kratom plant, which vary in potency based on their structural differences (1, 3, 4). 7-hydroxymitragynine is another derivative that makes up 2% of the kratom plant and has more than 40 times the potency of mitragynine (1). Mitragynine is an agonist of the μ-, κ-, and δ-opioid receptors with a higher affinity and potency than morphine (5). Its action on these opioid receptors allows this compound to exert analgesic and euphoric effects with the potential for respiratory depression (6). Compared with other opioid drugs, mitragynine is unique in its dose-dependent effects. At low concentrations it has stimulant effects, but behaves as a sedative at higher concentrations (1, 6). The exact doses for its stimulant, sedative, analgesic, and toxic thresholds remain unknown (6).

In Southeast Asia, kratom leaves (**Image 2**) are used by locals for both their medicinal effects against pain, diarrhea, fever, and as a recreational drug to reduce stress and enhance physical endurance and work capabilities (2, 5, 7, 8). Mitragynine has also been utilized as an affordable substitute to remedy withdrawal by those with opioid, amphetamine, and cannabis dependence (7, 9). The psychoactive compounds are most

Image 1: Kratom plant (Used under license from www.shutterstock.com).

commonly ingested by smoking, chewing, or brewing the kratom leaves (2, 10). Kratom-derived compounds are readily accessible via the Internet, which has aided in its spread to the United States, Europe, and Japan (11). In western countries, mitragynine is utilized as an herbal supplement for the self-management of chronic pain (2). Positive effects reported in western countries include euphoria, relaxation, increased energy, analgesia, and sensory enhancement (12). However, mitragynine's euphoric effect is addictive and is the reason for its abuse as a "legal" high. Its abuse potential is quickly becoming recognized (2, 11, 12).

Knowledge of the consequences of long-term mitragynine use is mostly derived from its countries of origin. In southeastern countries, chronic mitragynine use is complicated by weight loss, fatigue, constipation, dehydration, hand tremor, headache, and hyperpigmentation (2, 8). Adverse effects reported in western countries include abdominal pain, nausea/vomiting, pruritus, mouth and throat numbness, sedation, dizziness, visual disturbances, cholestatic jaundice, seizures, and coma (2, 12). Interestingly, kratom-induced toxicity and death have not been reported previously in Southeast Asia and this may be secondary to either the underreporting of cases or the development of tolerance amongst chronic users (2). Persistent users eventually develop dependence and tolerance, complicated by both physical and psychological withdrawal symptoms upon cessation, which resolves within one to three days (2, 8, 9, 13). The reported withdrawal symptoms range from the physical (e.g., rhinorrhea, lacrimation, myalgia, and arthralgia) to the psychological (e.g., aggression, hostility, and inability to work) (8). At present, standardized therapy for kratom dependence has not been elucidated (2).

Image 2: Kratom leaves (Used under license from www.shutterstock.com).

Although marketed as a herbal preparation with medicinal benefits as described above, mitragynine toxicity-associated fatalities have been reported in the literature (14-17). We present a case of a mitragynine-associated fatality in Canada in the setting of mixed drug toxicity, although this case is distinguished by a potentially independently fatal blood concentration of mitragynine as measured postmortem.

CASE REPORT

A 56-year-old woman with a history of chronic obstructive pulmonary disease (COPD) was found dead in bed after recent complaints of dyspnea and cough. Her prescribed medications consisted of Percocet (acetaminophen and oxycodone) and lorazepam. Scene investigation indicated that the number of pills remaining in each prescription bottle was noticeably less than if they had been taken as prescribed. She was also known to use cannabidiol oil drops and relatives reported that she would use a "methadone-like" powder of unknown composition that was obtained from Indonesia. Given the sudden unexpected nature of her death, a medicolegal postmortem examination was requested to determine her cause and manner of death.

The medicolegal postmortem examination was performed on the day after her body was discovered. External examination indicated that the decedent was a slightly overweight, middle-aged woman with a body mass index of 25.3 kg/m^2. A white residue was on the outside of her lips. Internal examination demonstrated cardiomegaly (heart weight, 532 g) with biventricular hypertrophy and mild atheromatous disease of the coronary arteries with no myocardial scars or established acute myocardial infarction. Lumenal pus was within the tracheobronchial tree and both lungs were heavy (left, 696 g; right, 658 g) and appeared hyperinflated with prominent fibrosis, consistent with the decedent's history of COPD, but no features of bronchopneumonic consolidation were evident. The esophagus contained white residue similar to that seen on the lips, but only bile-stained mucoid fluid was in the stomach.

The liver exhibited a prominent "nutmeg appearance," suggestive of congestive hepatopathy from passive venous congestion, attributable to right-sided heart failure. Fine and coarse granular cortical scarring of the kidneys was also noted. The urinary bladder contained 14 mL of urine.

Tissues from the main organs were processed into histological sections and examined microscopically. Cardiac blood, femoral venous blood, and urine were sent for standard toxicological analysis.

Histologic examination of the tissues revealed bilateral bronchopneumonia in a background of COPD changes in the lungs. Group B *Streptococcus* and *Staphylococcus aureus* were isolated from a swab of the pus in the trachea. Myocyte nuclear hypertrophy and patchy interstitial fibrosis were in the left ventricular myocardium. The liver exhibited mild portal inflammation with congestion of the terminal hepatic venules and perivenular regions. The kidneys exhibited scattered glomerulosclerosis and interstitial fibrosis.

Toxicological analysis of the femoral venous blood using a standardized panel detected oxycodone, lorazepam, and mitragynine; no other novel psychoactive substances were detected. Only oxycodone and lorazepam could be quantified by the reporting laboratory. The quantified concentrations of oxycodone (0.19 ± 0.01 mg/L) and lorazepam (63 ± 5 ng/L) were each not toxic in isolation, although the concentration of oxycodone was just under the reporting laboratory's threshold of fatality (0.21 mg/L). As the reporting toxicology laboratory did not possess a quantification method for mitragynine, the femoral venous blood sample was sent to a referral laboratory with such capability in the United States. The referral toxicology laboratory reported an independently fatal concentration of mitragynine of 2500 ng/mL, based on previously published values from mixed drug toxicity case reports (range of 20-1060 ng/mL). The reported concentration of lorazepam was in the range consistent with therapeutic use and the reporting laboratory indicted that no reliable reports of fatalities solely attributable to lorazepam exist.

Analytical Toxicology

The analytical method employed in the quantification of the mitragynine was as follows:

Sample Preparation

A whole blood sample of postmortem femoral venous blood was prepared for analysis via liquid-liquid extraction with 0.1 M Borax buffer (pH 10.4) and n-butyl chloride:ethyl acetate in 70:30 ratio. The generated supernatant was transferred to auto sampler vials. Extracts were dried and reconstituted with 500 μL 0.1% formic acid in acetonitrile.

Analysis

The analytical methods were validated on a Waters TQD Tandem Mass Spectrometer coupled to a Waters Acuity Ultra Performance LC system. The instrument was operated in positive electrospray, multiple reaction monitoring mode. Separation for blood method was performed on a Thermo Scientific BetaSil Silica-100 column, 2.1 x 100 mm column size, 5.0 μm particle size. An isocratic gradient of 10% ammonium formate buffer, pH 4.0 to 90% acetonitrile was used for chromatographic separation.

LC-MS/MS Transitions

The transitions identified for the quantitative and qualitative determination of mitragynine were 399.3>174.1 and 399.3>226.2. Transitions for D3-mitragynine were 402.3>177.1 and 402.3 >226.2. The quantified value of mitragynine was then extrapolated.

Overall, the positive toxicological findings in the femoral venous blood were as stated in **Table 1**.

Clinicopathological considerations indicated that her cause of death was combined mitragynine, lorazepam, and oxycodone toxicity (given the potential for synergistic effects of all three detected drugs on depressing the central nervous system) in conjunction with bronchopneumonia. In the context of the clinical history, the identified bronchopneumonia was more likely to have been a preexistent entity that had developed as a complication of COPD rather than as a secondary phenomenon of her mixed drug toxicity. Bronchopneumonia was therefore listed as a contributory cause of death. The mitragynine concentration was potentially independently fatal and death may have occurred in the absence of the other detected drugs (oxycodone and lorazepam) or underlying bronchopneumonia.

DISCUSSION

The mitragynine concentration detected in this case is the highest reported in kratom-related fatalities to date when compared to the previously published value of 1060 ng/mL (4). To our knowledge, this is the first reported case of mitragynine-associated fatality in Canada. Echoing previous reports, mitragynine was not the sole substance detected on toxicological analysis (4, 14-17). However, the measured concentration can be independently fatal, although the lethal and toxic ranges of mitragynine has not yet been definitively established (17). Studies in rat models have put forth a single dose of 200 mg/kg of oral mitragynine as the lethal cut off (18, 19). The oxycodone and lorazepam concentrations did not independently reach lethal ranges, but they would have contributed synergistically to the mitragynine-induced opioid agonistic effect to produce profound central nervous system and respiratory depression. The combination of the lethal range mitragynine concentration and its interaction with the two other depressant/sedative hypnotic drugs would

Table 1: Summary of Toxicologicy Results on Femoral Venous Blood and Their Respective Reference Values

Drug	Measured Concentrations	Lethal Reference Value
Oxycodone	0.19 ± 0.01 mg/L	>0.21 mg/L
Lorazepam	63 ± 5 ng/mL	Not reliably defined
Mitragynine	2500 ng/mL	20-1060 ng/mL (based on published case reports)

have been primarily responsible for the decedent's demise from a synergistic "drug-drug interaction" (11).

The addictive properties of mitragynine through its induced euphoria, mood enhancement, and improved performance portends its potential for abuse (2, 12). Dependence and tolerance develops in association with chronic consumption of high doses (8, 9). In a web-based anonymous survey, kratom users reported tolerance and an inclination to increase their intake to achieve the same positive effects (12). However, a safe ceiling dose for chronic consumption in humans has not been established (10). Given the lethal-range mitragynine level detected in our case, the decedent may have been a chronic consumer with high tolerance. There is no history of previous suicidal attempts, expressed suicidal ideations, or evidence of foul play to suggest this was an intentional overdose. At present, a standard treatment protocol for kratom dependence or antidote for acute toxicity has not been developed (2). In a mouse model, withdrawal symptoms were induced by naloxone administration following development of tolerance to 7-hydroxymitragynine, suggesting a potential antidote for mitragynine associated toxicity (20).

In Thailand, Malaysia, Bhutan, and Myanmar, the planting, sale, and purchase of kratom are illegal and penalties are imposed for those in possession of the substance (2). However, locals may obtain their supplies from known suppliers in the form of trees, prepared solutions, or tea (2, 8). Since 2005, kratom usage has been illegal in Australia (21). In western countries, mitragynine may be purchased via the Internet from unknown suppliers in the form of capsules, tablets, gums, leaves, and extracts for smoking, often with little knowledge of its quality and content (2, 22). Internet sales have marketed mitragynine as herbal remedies or dietary supplements without acknowledgement of its adverse effects and toxicities (2). The United States Drug Enforcement Administration has categorized kratom as a "Drug and Chemical of Concern" under consideration for making it illegal if supporting evidence of its addiction potential and health hazards become available (4, 23, 24). In Canada, kratom products were voluntarily recalled by its marketing company citing health risk concerns (25). Kratom-containing products are not authorized for sale by Health Canada, who recommended against its consumption in view of its adverse effects (25). Although marketed as a legal herb for its physiological and psychological benefits, its side effects and potential for lethality are increasingly recognized. The existing literature highlights the need for further supporting evidence and systematic review of kratom-associated health problems to help inform public health awareness and aid in development of regulations to prevent its adverse utilization (5). Furthermore, a reliable antidote for mitragynine-induced toxicity remains to be elucidated.

CONCLUSION

We present a case of an accidental death secondary to multidrug toxicity whereby mitragynine toxicity is primarily implicated. The measured mitragynine is likely independently fatal and appears to be the highest reported value in the medical literature to date. This is the first reported case of mitragynine-associated fatality in Canada. The only plausible source of the mitragynine lies in the report of the decedent's relatives that she would use a "methadone-like" powder of unknown composition which she had obtained from Indonesia, presumably via the Internet. Apart from contributing to the existing body of evidence on the adverse effects of mitragynine use, this case report is presented to help inform policy development to safeguard against the ease of accessibility of this easily available substance via the Internet to prevent further deaths.

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