Journal of Forensic Sciences / Volume 69, Issue 1 / pp. 355-358

CASE REPORT | Open Access

A case of fatal overdose involving both hydromor kratom

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First published: 27 September 2023
https://doi.org/10.1111/1556-4029.15394

Abstract

Kratom is a plant originating in Southeast Asia that ha dose-dependent stimulant and opioid effects. The mai in kratom is mitragynine, an alkaloid with affinity for th receptor. Toxicity and fatalities related to kratom use h substantially in recent years. In this case report, we de man who was found deceased in bed. The only signific autopsy was abdominal distension with >4L of ascites was performed on femoral blood which showed 79ng/ hydromorphone, 560ng/mL of mitragynine, and 240ng In addition, creatinine and urea in vitreous humor wer elevated, consistent with renal impairment. Death was hydromorphone toxicity with mitragynine being a con

Highlights

- Deaths related to kratom (mitragynine) use have

recent years.

- First report of combined hydromorphone and mitragynine toxicity causing death.
- Concomitant use of opioids and kratom may cause renal insufficiency.

1 INTRODUCTION

Mitragynine is an active alkaloid found in kratom, a herbal substance originating from the leaves of the Southeast Asian evergreen tree, *Mitragyna speciosa*. It is typically consumed for its stimulant and opioid-like effects [1-3] and can be brewed into a tea, chewed, smoked, or ingested in capsules [4]. Although kratom contains many alkaloids, mitragynine is thought to be one of the primary bioactive compounds. Specifically, mitragynine is a partial agonist for the human mu-opioid receptor [2, 3, 5].

Recently, kratom use has increased in Canada [6] and other western countries [7-9], owing to its legal status and ease at which it can be purchased including online websites, herbal supplement shops, and in smoke shops [10]. Common side effects associated with kratom use include tachycardia, agitation, drowsiness, seizures, respiratory depression, and coma [11]. Kratom has also been shown to cause drug-induced liver injury [12-14] and renal impairment [8, 15, 16]. Importantly, it has been associated with fatalities, both on its own [17] and in combination with other drugs [10, 18] including amitriptyline [19], quetiapine [20], and the opioids hydrocodone and morphine [21].

Here, we report the case of a fatal drug overdose involving both hydromorphone and mitragynine. This study was approved by the Research

Ethics Board of Horizon Health Network (file #2023-3257). Next of kin provided informed, written consent.

2 CASE HISTORY

In May 2022, a 44-year-old male was found deceased in bed. He was last seen alive around supper time the day before, but complained of poor appetite. He had not been eating for 4days. Empty capsules and medication bottles were found near the body. He recently filled two bottles of hydromorphone but both bottles were empty. Past medical history is notable for metastatic seminoma diagnosed 4years earlier that was treated with surgery and chemotherapy. He was seeing an oncologist regularly and there was no evidence of recurrence. He also had a history of schizoaffective disorder, bipolar type, but he was deemed stable by his psychiatrist. His medications included olanzapine, escitalopram, zopiclone, and hydromorphone (36mg daily). Upon further questioning of the decedent's father, the decedent had acquired a bag of brown powder from a friend a few months earlier and used the powder to make tea. The decedent had complained of abdominal pain and bloating in the days leading up to his death. He had taken more than the usual amount of hydromorphone to deal with the pain.

3 AUTOPSY FINDINGS

At autopsy, there was gross evidence of abdominal distension, but no jaundice, scleral icterus or other signs of acute liver failure. Upon dissection, there were>4L of ascites with associated pleural effusion. There was no evidence of bacterial peritonitis. There were no acute findings in the cardiorespiratory system to explain his death. Dissection of gastrointestinal system shows lack of food content. Dissection of the genitourinary system showed the presence of unilateral testis but otherwise no evidence of germ

cell tumor recurrence. There were a few calcified lymph nodes in the retroperitoneal fat, which had been known before and likely relates to his previous treatment. Upon microscopic examination of the liver, there was macro vesicular steatosis, but no evidence of acute hepatic necrosis or cirrhosis.

4 TOXICOLOGICAL FINDINGS

Four tubes of femoral blood (in vacutainers containing sodium fluoride as a preservative), vitreous humor, and urine were collected at autopsy for toxicology and chemistry testing. The vitreous humor was tested for a basic chemistry panel (glucose, beta-hydroxybutyrate, creatinine, and urea) on a Roche Cobas 8000® clinical chemistry platform. Vitreous humor was also tested for volatile alcohols (ethanol, isopropanol, methanol, and acetone) using a gas chromatograph with flame ionization detection (GC-FID). The femoral blood was sent to NMS Laboratories for an Expanded Postmortem Toxicology Panel. Specifically, blood was screened using both liquid chromatography/time of flight mass spectrometry (LC/TOF-MS) and GC-FID for a panel of >300 illicit and commonly prescribed substances as well as volatile alcohols as noted above.

Vitreous humor chemistry results are shown in Table 1. Femoral blood toxicology results are shown in Table 2. Hydromorphone was detected at a concentration of 79ng/mL and mitragynine was detected at a concentration of 560ng/mL. Finally, olanzapine was detected at a concentration of 240 ng/mL.

TABLE 1. Chemistry results in vitreous humor.

Analyte	Result

Glucose	0.3mmol/L
Beta-hydroxybutyrate	0.5mmol/L
Creatinine	330μmol/L
Urea	35.1mmol/L

TABLE 2. Toxicology results determined in femoral blood collected at autopsy.

Substance	Concentration
Hydromorphone-free	79ng/mL
Mitragynine	560ng/mL
Olanzapine	240ng/mL

5 DISCUSSION

Kratom is an evergreen plant native to parts of Southeast Asia. When administered in low doses, it exhibits stimulant-like effects however at higher doses, it exhibits opioid-like effects through its action at the mu-opioid receptor. Many adverse effects have been reported following use of this herbal supplement, including but not limited to seizures, psychosis, renal insufficiency, cardiovascular disease, and drug-induced liver injury.

Kratom use has increased in Canada [6] and other western countries [7-9]. Specifically, British Columbia, a province on the west coast of Canada, demonstrated an increase in kratom-related poison center calls from zero in

2012 to nine in 2019 [6]. The increase in use may be partly related to its legal status; kratom is currently legal in Canada as there are no laws that prohibit the use or sale of kratom in any of the provinces or territories. However, it is not approved for human consumption.

In this case, there was no obvious anatomic cause of death determined at autopsy. Vitreous humor glucose and beta-hydroxybutyrate were within normal postmortem ranges. The concentration of olanzapine detected in postmortem blood was attributed to therapeutic use. Vitreous humor creatinine and urea were both significantly elevated, consistent with renal impairment. The cause of death was attributed to hydromorphone toxicity with mitragynine use listed as a contributing factor. The manner of death was classified as a suicide as the coroner who investigated the death felt that given the history of cancer, pain, mental health disorder, and other circumstances including the presence of empty capsules and pill bottles in the vicinity of the body, suicide was the more probable than accidental. When questioned about possible kratom use, the next of kin in this case reported that the decedent had been taking a brown powder tea for the previous 6–8months that was thought to be kratom.

Concomitant use of kratom and other medications has increased in recent years. There are many reports of significant drug interactions between kratom and prescription medications including amitriptyline, quetiapine, hydrocodone, and morphine [10, 18-22]. LeSaint et al. reported a case involving a 21-year-old African American women who presented to the emergency department with nausea, vomiting, and left flank pain [21]. Serum creatinine was markedly elevated consistent with renal insufficiency. A urine drug screen was performed that identified the presence of morphine and hydrocodone in the patient's urine. She reported purchasing kratom on the internet and it was suspected that this product was contaminated with these two opioids. As no alternative cause could be identified for the renal

impairment, it was attributed to the kratom preparation she consumed. Interestingly, both creatinine and urea were significantly elevated in vitreous humor in the present case which is also indicative of renal insufficiency. Nonetheless, this patient did not have any history of renal disease and microscopically his kidneys only showed a benign cortical cyst.

Reports of renal impairment following kratom use are limited in the literature [8, 15, 16]. A 6-year retrospective review from the United States reported that renal failure was only found in 0.3% of cases reported to the poison control center [8]. A recent study by Jasim et al. demonstrated that kratom users are predisposed to proteinuria, as evidenced by an increase in urinary albumin compared to heathy controls [16]. They hypothesized that this may make kratom users more susceptible to glomerulonephritis. Antony et al. reported the development of acute tubular necrosis secondary to pigment nephropathy in a 70-year-old man with kratom-associated cholestatic liver injury [15]. In the present case, the decedent did not have any history of previous renal disease; bloodwork done within 2years of his death showed normal serum creatinine levels and eGFR. No signs of chronic renal disease were observed at autopsy either. Therefore, it is possible that he developed kidney disease secondary to kratom use. As renal impairment can impact clearance of hydromorphone, this may contribute to the toxicity associated with concomitant use of both of these drugs. While the incidence of renal impairment following kratom use is low, this case report adds to the growing body of literature that suggests this is an important adverse effect that warrants further investigation.

A lethal threshold for blood mitragynine has not yet been unequivocally established. In a recent study, blood concentrations from a combination of hospitalizations, human performance, and postmortem case work ranged from 5.0 to 11,000ng/mL [10]. The mean and median concentration in postmortem cases specifically was 360 and 120ng/mL, respectively.

Interestingly, the mean and median concentration of mitragynine in impaired driving cases was significantly lower at 133 and 62ng/mL, respectively [10]. In another series of postmortem cases, the blood concentration of mitragynine ranged from 3.5 to 3600ng/mL [18]. Lower concentrations of mitragynine in postmortem blood have been attributed to death when detected in combination with other substances [22] compared to the detection of mitragynine alone [10]. It has been suggested that mitragynine concentrations in between 100 and 500ng/mL should be considered as possibly contributing to death while concentrations >1000 ng/mL are more often associated with causing death [22].

To the best of our knowledge, this is the first time that a fatality related to concomitant use of mitragynine and hydromorphone has been reported. Others have shown an increase in the detection of mitragynine with other prescription opioids [10]. Specifically, Papsun et al. reported a significant increase in the presence of fentanyl in mitragynine-positive cases from 33% in 2018 to 62% in 2022 [10]. They also reported steady increases in detection of hydrocodone, tramadol, and buprenorphine in mitragynine-positive cases too. While the role that mitragynine plays in contributing to death when co-ingested with other opioids is not fully understood, it is thought that mitragynine may exacerbate respiratory depression and lead to cardiopulmonary failure through CNS depression effects [23]. In addition, this case report adds to the growing body of literature which suggests that renal impairment may play a role in the morbidity and mortality associated with kratom use too.

In conclusion, we have presented a fatal case of hydromorphone and kratom toxicity that resulted in renal impairment and death. This shows that herbal, over-the-counter (OTC) substances can play an important role in toxicologic deaths. When the clinical history is notable for the use of OTC/herbal compounds, toxicology laboratories should broaden their scope of testing to

include newly “in fad” compounds such as kratom.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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