Forensic Science, Medicine and Pathology (2019) 15:110–113
https://doi.org/10.1007/s12024-018-0049-9

CASE REPORT

Fatal combination of mitragynine and quetiapine – a case report with discussion of a potential herb-drug interaction

Rhome L. Hughes [1]

Accepted: 5 November 2018 / Published online: 29 November 2018

Abstract

Kratom is a plant with dose-dependent mixed stimulant and opioid properties whose pharmacologic characteristics and social impact continue to be described. The main active isolate of kratom is mitragynine, an indole-containing alkaloid with opioid-like effects. Kratom toxicity and kratom-associated fatalities have been described, including those in association with additional drugs. In this paper we describe the case of a 27-year-old man who was found deceased with a toxic blood concentration of quetiapine in conjunction with the qualitative presence of mitragynine. Investigative and autopsy findings suggested perimortem hyperthermia and seizure-like activity. Kratom toxicity and kratom-associated fatalities are being increasingly reported. Experiments with kratom extracts have shown inhibitory effects upon hepatic CYP enzymes, leading to previous speculation of the potential for clinically significant interactions between kratom and a wide array of medications. Herein is described a fatal case of quetiapine toxicity complicated by mitragynine use. The potential ability of mitragynine to alter the pharmacokinetics of a prescription medication via inhibition of its hepatic metabolism is discussed.

Keywords Kratom · Mitragynine · Quetiapine · Overdose · CYP

Introduction

Kratom is a plant native to areas of Southeast Asia, which has long been consumed by indigenous people for its mixed stimulant- and opioid-like effects [1–5]. The main active alkaloid isolate of kratom is mitragynine, which has an array of pharmacologic actions, including those at mu-opioid receptors [1, 2, 4–7]. Kratom use within the U.S. is reportedly on the rise, popularized by its pain-relieving abilities and use in the self-management of opioid withdrawal, with a parallel increase in the reported number of cases describing kratom-associated toxicity; several such cases have resulted in death [2, 6–9]. Physicians (including forensic pathologists) should be aware of the growing availability and increasing use of kratom, and for the potential of kratom-associated toxicity, including herb-drug interactions.

✉ Rhome L. Hughes
rhome.hughes@und.edu

[1] University of North Dakota School of Medicine and Health Sciences, 1301 N. Columbia Rd (Room W430), Grand Forks, ND 58203, USA

Case report

A 27-year-old man with a past medical history significant for Asperger Syndrome, bipolar disorder, and substance abuse was found deceased inside his secured residence. The decedent was discovered lying supine on his bed. He was shirtless but clad in pajama pants. On the bathroom floor, adjacent to a bathtub filled with water, were a wet pair of blue jeans and a wet t-shirt. Present within the residence were multiple prescription medications. A metal vaporizer (inhalation device) was present on the bed adjacent to the body.

Autopsy examination showed a well-developed, well-nourished man with no external evidence of acute blunt force or penetrating trauma. Findings included dark fluid emanating from the mouth, clenched fists, and a 2 cm focus of intramuscular hemorrhage on cut sections of the tongue. Postmortem forensic toxicology was performed on subclavian blood. Valproic acid was quantitatively positive at 8.8mcg/mL (high performance liquid chromatography). Quetiapine was quantitatively positive at 12000 ng/ml (high performance liquid chromatography / tandem mass spectrometry). Mitragynine was qualitatively positive (high performance liquid

chromatography / tandem mass spectrometry). The cause of death was ruled as acute toxic effects of quetiapine complicated by mitragynine use. The manner of death was classified as accident.

Discussion

Kratom (*Mitragyna speciosa*) is a tree-like plant found in tropical and subtropical regions of Asia, particularly Thailand and Malaysia [1–5]. In its indigenous range, the plant has been reportedly used for hundreds of years for its complex, dose-dependent effects (low-to-moderate doses produce mild stimulant effects, while moderate-to-high doses produce opiate-like effects), typically by ingestion of the raw leaf or consumption of teas brewed or steeped from the leaves [2–5]. In the United States, there has been a reported recent increased level of kratum use, particularly among college-aged populations, both for the self-management of pain and treatment for opiate withdrawal [2, 10]. While kratom is not scheduled under the Controlled Substances Act, in 2010 the Drug Enforcement Agency did include it in the Drugs and Chemicals of Concerns list, citing "there is no legitimate medical use for kratom in the U.S." [3, 4, 6]. While kratom remains legal – and is readily available in "head- "or "smoke-shops," or via the internet – several states have moved to have the drug banned by making it a controlled substance (state-by-state information on the legal status of kratom can be accessed online through organizations such as the American Kratom Assocation) [2].

Of kratom's numerous (20-plus) pharmacologically active alkaloid isolates, mitragynine is both the most abundant and extensively characterized, and widely regarded as producing the majority of the plant's psychoactive effects [1, 2, 4, 6, 10]. Mitragynine has reported stimulant effects at low doses (1–5 g of raw leaves), with opioid-like effects at high doses (5–15 g of raw leaves) attributed to agonist activity at Mu and Kappa-opioid receptors [2, 6, 10]. Additional reported pharmacologic effects of mitragynine are reported in Table 1. Chronic mitragynine use is associated with physical dependence and potentially severe withdrawal symptoms resembling those of opioid withdrawal, occurring 12 to 24 h after last use [2, 6].

Table 1 Pharmacology of mitragynine [2]

- Main activity is on μ receptors, creating opiate and analgesic effects and physical dependence.
- Activates descending noradrenergic and serotonergic pathways in spinal cord.
- Stimulates postsynaptic α_2-adrenergic receptors.
- Blocks stimulation of 5-hydroxytryptamine$_{2A}$ receptors.
- Inhibits LPS-stimulated cyclooxygenase-2 expression and prostaglandin E2 production.

Over the past several years, there has been an increase in case reports detailing adverse reactions associated with kratom use [2, 7]. The toxic effects associated with kratom appear to be related to the drug's stimulant and opioid activities, with stimulant-effects manifesting as anxiety, irritability, and aggression, and opioid-effects presenting as sedation, nausea, constipation and itching [2]. Additional effects include dry mouth, changes in urination, vomiting, and weight loss [5]. Cardiotoxic effects have also been postulated [8].

Of a more serious concern, several reports have emerged of kratom-associated seizures, typically resulting from high-dose usage, either alone or in combination with other drugs [2, 5, 10, 11]. Multiple kratom-associated deaths have been reported [5, 8, 9]. A 2018 statement from the FDA reported the number of Kratom-associated deaths as 44 [7]. Of interest, multiple described fatalities also contained therapeutic levels of prescription medications with pharmacologic actions distinct from opiate receptor activation, highlighting the difficulty in assessing an herbal agent's safety when there remains a lack of understanding of how compounds in that agent interact with other medications, drugs or herbal supplements [2].

In the present case, the decedent's valproic acid level was below reported therapeutic levels (and thus considered non-contributory to his death) [12, 13]. His quetiapine level of 12 mg/L was within the toxic/lethal range [12, 13]. Reliable toxic reference standards for mitragynine have yet to be established; however, reported concentrations of mitragynine in postmortem blood samples range from 230 to 1006 μg/L [9]. The assumed symptomology preceding his death were hyperthermia/fever (as suggested by the pile of wet clothing adjacent to a bathtub full of water), and seizure/convulsions (as evidenced by the intramuscular hemorrhage of the tongue). While the toxic effects of quetiapine could in and of themselves account for these symptoms via a neuroleptic malignant syndrome-like reaction, mitragynine is likewise associated with the development of seizures (as described above) and further hypothesized to produce hyperthermic-type effects via activation of mu opioid receptors [12, 14, 15]. As such, it is furthermore plausible that the decedent's symptomology was the result of a combined and/or synergistic reaction to quetiapine and mitragynine.

Of further interest to the case, assessment of the decedent's quetiapine medication, as located in his residence, did not reveal any significant discrepancies in pill quantities that might reliably account for his postmortem blood quetiapine level of 12 mg/L (i.e. no large quantities of pills were detected missing). By comparison, a previously published report demonstrated a serum quetiapine level of 12.7 mg/L after the ingestion of 100 tablets (200 mg each) [16]. However, it should be stated clearly that in the present case the actual ingestion

quantity of neither quetiapine or kratom is known to any degree of certainty.

Quetiapine is known to be extensively and predominately metabolized in the liver by cytochrome P450 3A4 (CYP3A4), largely to inactive metabolites which are then renally excreted (with less than 1% of the parent compound excreted unchanged) [17, 18]. It has been demonstrated that strong inhibitors of CYP3A4 have profound effect on plasma concentrations and clearance rates of quetiapine; co-administration with ketoconazole (a CYP3A4-inhibitor) produces a 3.35-fold increase in mean quetiapine plasma C_{max}, and decreases clearance by 84% [19]. Mitragynine has reported inhibitory effects on multiple cytochrome P450 enzymes, including CYP2D6 (noncompetitive), CYP2C9 (noncompetitive), and CYP3A4 (competitive); these three enzymes are all members of the small core group of cytochrome P450 enzymes that are responsible for the metabolism of 90% of all drugs, with the two most significant being CYP3A4 and CYP2D6 [10, 20, 21]. It has been previously suggested that this inhibitory action of mitragynine upon CYP enzymes may produce clinically significant interactions with other drugs [10, 20]. As such – given the described action of mitragynine upon CYP3A4, the enzyme responsible for 89% of quetiapine's metabolism [22] – it may be that in this case the decedent's quetiapine level was affected by an inhibitory effect upon the drug's metabolism and clearance due to concomitant mitragynine use.

A second mechanism by which mitragynine could alter concomitant quetiapine levels is via inhibition of cellular transport proteins, such as P-glycoprotein (P-gp), a membrane-bound efflux pump located in excretory tissues and blood-tissue barriers [23, 24]. P-gp actively transports substrates from inside to outside of cells, thus serving to promote a substrate's elimination, with alterations in P-gp activity effecting serious drug-drug interactions. Mitragynine has been identified as a clinically relevant P-gp inhibitor [23], and quetiapine has been identified as a P-gp substrate [24]. Thus, there exists at least the potential that P-gp-mediated elimination of quetiapine could be hindered by concomitant mitragynine use, producing elevations in quetiapine levels, although additional investigation would be necessary to validate this claim.

In conclusion, the case reported herein demonstrates a fatal combination of quetiapine and mitragynine, and highlights a potential herb-drug interaction postulated upon mitragynine-mediated interference with quetiapine's metabolism and/or elimination. While neither the ingestion quantity of quetiapine nor kratom is known in this case, the circumstances of the case are supportive of the notions of altered quetiapine metabolism and clearance, and synergetic symptomology, lending support to previously advanced concerns for mitragynine-associated herb-drug interactions. Given that mitragynine has additional inhibitory effects on other enzymes (including CYP2D6 and CYP2C9), the overall importance of these enzymes to the metabolic inactivation of a large array of prescription medications, and the number of additional know prescription drugs that are P-gp substrates, then similar interactions between mitragynine and other medications might be expected. Further study is needed to fully elucidate mitragynine's effect upon the human body, with careful attention paid to potential herb-drug interactions.

Key points

1. Kratom is a plant with mixed stimulant- and opioid-like effects.
2. The main alkaloid isolate of kratom is mitragynine, which has pharmacologic action at mu-opioid receptors.
3. Reports of kratom use and kratom-associated complications are on the rise, including multiple reported fatalities.
4. Mitragynine has been experimentally demonstrated to display inhibitory effects on hepatic CYP enzymes and the P-gp transport protein.
5. Kratom is commonly used in combination with other drugs, and potential herb-drug interactions deserve consideration and investigation.

Compliance with ethical standards

Conflict of interest None.

Ethical approval Not applicable.

Informed consent Not applicable.

References

1. Trakulsrichai S, Sathirakul K, Auparakkitanon S, Krongvorakul J, Sueajai J, Noumjad N, et al. Pharmacokinetics of mitragynine in man. Drug Des Devel Ther. 2015;9:2421–9.
2. Prozialeck W, Jivan J, Andurkar S. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J Am Osteopath Assoc. 2012;112:792–9.
3. Pantano F, Tittarelli R, Mannocchi G, Zaami S, Ricci S, Giorgetti R, et al. Hepatotoxicity induced by "the 3Ks": kava, kratom and khat. Int J Mol Sci. 2016;17:580.
4. Kratom (Mitragyna speciosa korth). 2013. http://www.deadiversion.usdoj.gov/drug_chem_info/kratom.pdf. Accessed 7 July 2016.
5. Castillo A, Payne JD, Nugent K. Posterior reversible leukoencephalopathy syndrome after kratom ingestion. Proc (Baylor Univ Med Cent). 2017;30:355–7.
6. Galbis-Reig D. A case report of kratom addiction and withdrawal. WMJ. 2016;115:49–52.
7. Food and Drug Administration. 2018. Statement for FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse [Press release]. https://www.

fda.gov/newsevents/newsroom/pressannouncements/ucm595622.htm. Accessed 2 Aug 2018.
8. Aggarwal G, Robertson E, McKinlay J, Walter E. Death from kratom toxicity and the possible role of intralipid. J Intensive Care Soc. 2018;19:61–3.
9. Domingo O, Roider G, Stover A, Graw M, Musshoff F, Sachs H, et al. Mitragynine concentrations in two fatalities. Forensic Sci Int. 2017;271:e1–7.
10. Warner ML, Kaufman NC, Grundmann O. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int J Legal Med. 2016;130:127–38.
11. Nelsen JL, Lapoint J, Hodgman MJ, Aldous KM. Seizure and coma following kratom (mitragynine speciosa korth) exposure. J Med Toxicol. 2010;6:424–6.
12. Baselt RC. Disposition of toxic drugs and chemicals in man. 8th ed. Foster City (CA): Biomedical Publications; 2008.
13. Molina DK. Handbook of forensic toxicology for medical examiners. Boca Raton: CRC Press; 2010.
14. Gortney JS, Fagan A, Kissack JC. Neuroleptic malignant syndrome secondary to quetiapine. Ann Pharmacother. 2009;43:785–91.
15. Raffa RB. Kratom and other mitragynines: the chemistry and pharmacology of opioids from a non-opium source. Boca Raton: CRC Press; 2015.
16. Harmon TJ, Benitez JG, Krenzelok EP, Cortes-Belen E. Loss of consciousness from acute quetiapine overdosage. J Toxicol Clin Toxicol. 1998;36:599–602.
17. Devane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clin Pharmacokinet. 2001;40:509–22.
18. Bakken GV, Rudberg I, Christensen H, Molden E, Refsum H, Hermann M. Metabolism of quetiapine by CYP3A4 and CYP3A5 in presence or absence of cytochrome B5. Drug Metab Dispos. 2009;37:254–8.
19. Grimm SW, Richtand NM, Winter HR, Stams KR, Reele SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. Br J Clin Pharmacol. 2006;61:58–69.
20. Hanapi NA, Ismail S, Mansor SM. Inhibitory effect of mitragynine on human cytochrome P450 enzyme activities. Pharm Res. 2013;5:241–6.
21. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician. 2007;76:391–6.
22. Hasselstrom J, Linnet K. In vitro studies on quetiapine metabolism using the substrate depletion approach with focus on drug-drug interactions. Drug Metabol Drug Interact. 2006;21:187–211.
23. Meyer MR, Wagmann L, Schneider-Daum N, Loretz B, de Souza Carvalho C, Lehr CM, et al. P-glycoprotein interactions of novel psychoactive substances – stimulation of ATP consumption and transport across Caco-2 monolayers. Biochem Pharmacol. 2015;94:220–6.
24. Schmitt U, Kirschbaum KM, Poller B, Kusch-Poddar M, Drewe J, Hiemke C, et al. In vitro p-glycoprotein efflux inhibition by atypical antipsychotics is in vivo nicely reflected by pharmacodynamic but less by pharmacokinetic changes. Pharmacol Biochem Behav. 2012;102:312–20.