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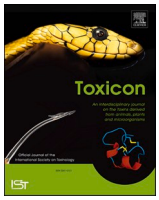

Case report

Mitragyna speciosa (Kratom) poisoning: Findings from ten cases

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ABSTRACT

Kratom is a mixture of compounds that are present in the leaves of the tropical tree Mitragyna speciosa. It is used as a psychoactive agent with both opiate and stimulant-like effects. In this case series we describe the signs, symptoms, and the management of kratom overdose in the prehospital setting and in intensive care. We retrospectively searched for cases in the Czech Republic. Over 36 months we found 10 cases of kratom poisoning, which healthcare records were analyzed and reported as per CARE guidelines. The dominant symptoms in our series were neurological and included quantitative (n = 9) or qualitative (n = 4) disorder of consciousness. Signs and symptoms of vegetative instability [hypertension (n = 3) and tachycardia (n = 3) vs. bradycardia/cardiac arrest (n = 2), mydriasis (n = 2) vs. miosis (n = 3)] were noticed. Prompt response to naloxone in two cases and lack of response in one patient were observed. All patients survived and the effect of intoxication wore off within two days. Kratom overdose toxidrome is variable and, in keeping with its receptor physiology, consists of signs and symptoms of opioid-like overdose, sympathetic overactivation and serotonin-like syndrome. Naloxone can help to avoid intubation in some cases.

1. Introduction

Mitragyna speciosa is a tropical tree common in Southeast Asia (Indonesia, Malaysia, and Thailand). Its extracts known as kratom are being used as a psychoactive substance with both opiate and stimulant-like effects (Patel et al., 2021). Kratom is sold as dried leaves, powder (also in capsules or tablets), chewing gum or other products. It can be chewed, drunk as a tea or smoked. It has been used in traditional medicine for millenia (Forrester, 2013; Reinert et al., 2020), but in Europe and the USA kratom use seems to be rapidly increasing. While there were no kratom exposures reported before the year 2008 in the USA (Forrester, 2013), over 2 million adults are estimated to have taken some form of kratom in 2021 (Schimmel et al., 2021). In Europe, kratom is classified as an illegal substance in Denmark, Finland, Ireland, Latvia, Lithuania, Poland, Romania and Sweden), but is not controlled at all in others (e.g. the Czech Republic) (Reinert et al., 2020). The World Health Organization's Executive Committee on Drug Dependency investigated the risks of kratom in 2021 and advised keeping this substance under surveillance, but declined to recommend a ban in view of the lack of evidence of the risk for public health.

Although the presentations of kratom users at hospitals represent only the tip of the iceberg and detailed registry data are lacking, kratom use appears to be increasingly popular in Europe, either recreationally, typically by young adults, or as self-treatment of a range of diseases, such as musculoskeletal pain or chronic wounds, typically in the elderly (Hassan et al., 2013). It seems that long-term use of kratom is associated with addiction but with no long-term cognitive effect (Singh et al., 2019). The incidence of side effects, mostly neurological and cardiovascular, increases with age, reaching 20% in adults over 70 years old, possibly due to interaction with other medications (Graves et al., 2021). Given the relative novelty and heterogeneity of the symptoms, the diagnosis of kratom overdose or side effects in emergency departments can be challenging. No data are available from prospective clinical trials on management either.

In this retrospective study we aimed to describe the clinical course of kratom poisonings confirmed by patients. To raise awareness about this

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diagnosis and aid clinicians managing it, we emphasize the initial presentation in the prehospital setting and analyze the response to the empirical treatments that were chosen.

2. Material and methods

We have retrospectively searched the electronic health records of the Emergency Medical Services (EMS) of three geographical regions in the Czech Republic (Moravian-Silesian, South Moravian, and Prague regions) covering an area with over 2.6 million inhabitants. We have only included cases from 2019 to 2022, in which the use of kratom has been confirmed by the patients themselves. We excluded cases lacking confirmation of kratom use. The Ethical Committee of Karlovy Vary EMS reviewed the report and approved the study. Given the epidemiologic and retrospective nature of the study, which uses deidentified data, the need for informed consent was waived (Decision No. ZZSKVK/EK/012022). We only used descriptive statistics and the report is compliant with CARE guidelines for reporting case series (Gagnier et al., 2013).

3. Results

Ten cases of confirmed kratom overdose were found in total; there was no death associated with confirmed or suspected kratom overdose. Baseline characteristics, initial presentation as well as the summary of treatments given and responses are shown in Table 1. Detailed descriptions of individual cases are in the Supplementary Appendix. Based on the history, clinical chemistry results and urinary toxicology screen, seven patients were co-exposed to other substances such as ethanol (n = 2), benzodiazepines (n = 2), opioids (n = 2), cannabinoids (n = 1) or methamphetamine (n = 1).

The most common symptom was a quantitative disorder of consciousness, often preceded by confusion or delirium. One patient was in cardiac arrest, five patients required orotracheal intubation, and all patients were admitted to an intensive care unit for monitoring and general supportive care. Of note, 0.4 mg of naloxone in two cases (nos. 4 and 10) resulted in prompt improvement of the disorder of consciousness, which would have otherwise required endotracheal intubation.

4. Discussion

Ten case reports are presented as a series to introduce the different signs and symptoms of kratom overdose. Our patients were young adults, who mostly took kratom orally for recreational purposes and it is likely that adverse effects occurred as a result of either (1.) accidental overdose or (2.) the interaction of kratom with other substances used, known or unknown to healthcare providers, or (3.) the possibility of substance adulteration. The dominant symptoms in our series were neurological and included quantitative (n = 9) or qualitative (n = 4) disorder of consciousness or headache (n = 1). These were also the most common triggers for calling the emergency medical service. Secondly, signs and symptoms of vegetative instability with a mix of sympathetic [hypertension (n = 3), tachycardia (n = 3), mydriasis (n = 2)] and parasympathetic syndromes [miosis (n = 3), vomiting (n = 2), bradycardia/cardiac arrest (n = 2)] were noticed. This is in keeping with previously published cases (Patel et al., 2021; Tobarran et al., 2022; LeSaint et al., 2022; Sekar et al., 2022; Regan and Papadakos, 2021) and review papers (Forrester, 2013; Reinert et al., 2020; Singh et al., 2020; Davidson et al., 2021; Zuberi et al., 2019; Overbeek et al., 2019; Hall and Hall, 2021). All our patients survived.

Kratom is composed of numerous indole alkaloids (paynantheine, speciogynine, speciociliatine, mitaciliatine, corynoxine, etc.). The most studied alkaloid is mitragynine and its metabolite 7-α-hydroxymitragynine, which are responsible for the stimulant and euphoric effect (Reinert et al., 2020; Sharma and McCurdy, 2021; Hiranita et al., 2022; Tanna et al., 2022). Mitragynine is the most abundant and 7-α-hydroxymitragynine (7-OH-mitragynine) the most potent (Reinert et al., 2020). The effect of kratom occurs 5–10 minutes after ingestion and lasts up to 5 h. It is dose dependent and chronic users might require increasing dosages for the analgesic effects (Reinert et al., 2020; Singh et al., 2020; Müller et al., 2020, 2021). The dose up to 5 g is associated with stimulation (increased sociability, alertness, and energy), 5–15 g comes with opioid-like effects (Reinert et al., 2020). Mitragynin and 7-OH-mitragynine act as partial agonist on the mu-opioid receptor and as antagonists at the other opioid receptors and it may also stimulate pre- and post-synaptic alpha-2 adrenergic receptors, dopamine D2, and block stimulation of serotonin 2A receptor (5-HT2A) (Reinert et al., 2020). Due to very low renal clearance of mitragynine and a large volume of distribution, enhanced elimination procedures such as dialysis may not be effective in exposure treatment (Reinert et al., 2020). The metabolism of mitragynine in humans occurs via hydrolysis of the side-chain ester, O-demethylation of the methoxy groups, oxidative and/or reductive transformations, and the formation of glucuronide and sulphate conjugates (Reinert et al., 2020).

Putting receptor physiology together with the clinical picture observed in this case series, we can infer that kratom toxidrome is a mixture of the following components:

- opioid syndrome with depressed consciousness or coma, bradypnea, miosis, and vomiting;
- sympathetic overactivation syndrome: hypertension, tachycardia, and mydriasis;
- serotonin-like syndrome that includes agitation, restlessness, confusion, myoclonus, and vomiting.

Indeed, the signs and symptoms of these syndromes often offset each other, and, in turn, clinical presentations of each individual patient are variable and depend on individual health conditions, tolerance, dose, and co-ingested substances. Although it is possible to detect 7-α-hydroxymitragynine in serum and in urine in a toxicology lab by liquid chromatography with mass spectrometry (Palasamudram Shekar et al., 2019), these methods can rarely be used in clinical practice at the bedside. We believe that – despite the variability of kratom toxidrome – our data can help clinicians to be aware of the possibility of this diagnosis in daily practice.

As with most other CNS depressing drugs, the key component of kratom overdose treatment is good supportive care in an ICU, aimed at preventing complications before the kratom effects wear off. The United Kingdom National Poisons Information Service recommends naloxone as an antidote, as well as ionotropic and vasopressor support and intralipid to improve cardiovascular function (Reinert et al., 2020; Aggarwal et al., 2018). In keeping with that, the opioid-like component of kratom toxidrome was antagonized by the use of naloxone, which seemed to have prevented the need for intubation in our two cases as well as in those reported by others (Reinert et al., 2020; Overbeek et al., 2019). One of our patients did not respond to naloxone. This phenomenon has already been reported (Palasamudram Shekar et al., 2019), suggesting the more complex nature of kratom's CNS depressing effects. Apart from biological plausibility in binding some of the lipophilic alkaloids present in kratom, lipid infusion is a low-risk treatment, which has been reported to temporarily improve cardiorespiratory function in a 26-year-old man who later died of kratom overdose (Aggarwal et al., 2018). There are no further data on intralipid use in this indication, and it has not been attempted in our case series. In addition, labetalol has been used with success to treat sympathetic overactivation.

4.1. Limitations

Before drawing any conclusions, the limitations of our study should be noted. Firstly, our case series consists of patients who survived and self-reported kratom use, but none of these patients have been directly tested for the presence of the substance in the bloodstream. It is possible that some of the patients in the case series were poisoned by various

Table 1
Baseline case subject characteristics, context, initial presentation, and management of kratom overdose.

Age/Sex	Time after use [h]	Form of exposure	Co-exposure	Reason for EMS call	Site	Airway compromise	RR [min^{-1}]	SpO_2 [%]	Naloxone		ETT	BP [mmHg]	HR [min^{-1}]	GCS	Miosis	Other symptoms
									Dose	Resp.						
21/F	12–24	PO extract ('tea')	No	Confusion	Home	No	14	99	–	–	Yes	100/60	96	4-5-1		Psychotic
36/M	12	Unknown	No	Unresponsive	Home	Yes	16	100	0.4 mg	No	Yes	180/110	95	2-1-1	Yes	Vomiting
18/M	24	PO extract ('powder')	Cannabis, wasp sting	Unresponsive	Home	No	–	–	0.2 mg	Yes	–	–	30	Unk. *	Yes	Anaphylactoid reaction
19/F	1	Unknown	Ethanol	Unresponsive	Home	No	12	99	0.4 mg	Yes	–	140/80	120	2-2-4		none
25/M	Unknown	PO extract ('tea')	Clonazepam	Unresponsive	Home	No	7	70	–	–	Yes	120/70	102	1-1-1	Yes	none
27/M	12	PO extract ('tablets')	Heroin, caffeine	Unresponsive	Home	No	4	97	0.4 mg	Yes	–	200/110	106	1-1-1	Yes	none
24/M	<12	Unknown	Clonazepam, diazepam, opioids	Suicide attempt	Police office	No	15	98	–	–	–	140/100	130	4-5-6		Psychotic
23/M	Unknown	Unknown	Ethanol, COVID-19	Cardiac arrest	Home	Yes	0	0	–	–	Yes	0	0	1-1-1	Yes	none
45/M	1	PO powder	Methamph.	Unresponsive	Home	Yes	6	68	–	–	Yes	200/100	100	1-1-1		none
23/M	1	IN extract ('powder')	No	Unresponsive	Home	No	7	90	0.2 mg	Yes	–	170/100	110	1-1-3	Yes	none
23.5 (21.5; 26.5)						*3*	*7 (6; 14)*	*97 (70; 99)*	*5*	*4*	*5*	*Sys 140 (120; 180) Dias 100 (77; 102)*	*101 (95; 109)*	*4 (3; 8)*	*6*	

Note: BP = blood pressure, EMS = emergency medical service, ETT = endotracheal tube placed, PO = per os, IN = intra nasally, RR = respiratory rate, Resp. = response, SpO2 = saturation of haemoglobin with oxygen measured by pulse oximetry, HR = heart rate, GCS = Glasgow Coma Scale ranging from 3 to 15 points, where 3 is a deep coma and 15 normal level of consciousness, Methamph. = methamphetamine, Miosis = pupil size 1–2 mm. Summary data presented as Median (Interquartile range).*Patient reported to be only responsive to painful stimuli.

illegal substances, or that the substance they have had exposure to in fact contained very little or no mitragynine and 7-OH-mitragynine. The clinical picture might indeed have been altered by co-ingested substances. On the other hand, we might have missed patients who died of or survived kratom poisoning, which was not considered or detected. This might explain why our cohort does not include elderly patients, in whom kratom poisoning might not have been considered by the clinicians. In addition, we have not systematically collected data on the source where the kratom was obtained from and whether it might have been adulterated.

Given the inherent uncontrolled before-after nature of the observation of the effect of therapeutic interventions, no definite conclusions should be drawn as to whether these interventions are effective or not. On the other hand, this is the only information available to clinicians, a situation not uncommon in the field of clinical toxicology.

5. Conclusion

Kratom overdose – a relatively new and rapidly spreading psychoactive substance in Europe – often occurs in young adults who present with a disorder of consciousness and a mixture of signs and symptoms of opioid-like, sympathetic and serotonin syndromes. Although direct detection tests of mitragynine and 7-OH-mitragynine in the bloodstream exist, they rarely can be used for clinical purposes. Naloxone can be tried to avoid the need for intubation and labetalol to control the sympathetic syndrome. Intralipid infusion is also recommended, but there are no data or practical experience with this treatment.

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Ethics approval and consent to participate

The study was approved and written consent to participate was waved by the ethics committee of the EMS of the Karlovy Vary Region under Approval Number: ZZSKVK/EK/012022 on 27 September 2022.

Credit author statement

DP: Conceptualization, Methodology, Formal analysis, Resources, Writing – original draft; **MS:** Conceptualization Resources, Writing – Reviewing and Editing; **PC:** Resources, Writing – Reviewing and Editing; **RS:** Methodology, Formal analysis, Writing – original draft; **SP:** Writing – original draft; **FD:** Conceptualization, Methodology, Supervision, Writing – Reviewing and Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.toxicon.2023.107054.

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