Case report

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Death from Kratom toxicity and the possible role of intralipid

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Abstract

We present the case of a 26-year-old man who was brought into our emergency department in cardiorespiratory arrest, having taken Kratom 24 h previously. Despite multi-organ support, he deteriorated and died from cardiorespiratory failure and hypoxic brain damage 12 h later. Lipid emulsion was given, with significant temporary improvement in the cardiorespiratory failure. Kratom is derived from Mitragyna speciosa, a tropical deciduous and evergreen tree in the coffee family, and is native to Southeast Asia, and its leaves are used as a legal high in some parts of the world. Here, we review the pharmacochemistry of the drug, and wish to highlight that the effects of Kratom may not be as benign as are commonly reported, and the possible role of intralipid in managing the Kratom toxicity in this case.

Keywords

Mitragyna, lipid emulsion, toxicity, hypoxia, brain

Introduction

Kratom is a naturally occurring plant extract which is widely used for its euphoric properties. It is generally reported to be safe.

Case history

A 26-year-old man was admitted to the emergency department (ED) at our hospital, having been found in cardiorespiratory arrest. Prior to this admission, he had no medical history, and took no regular prescribed medication. There was a history of ingestion of an unknown quantity of Kratom 24 h previously.

The rhythm during the cardiorespiratory arrest was primarily pulseless electrical activity (PEA), with a brief period of ventricular arrhythmia. The arrest was managed according to standard protocol, with the addition of sodium bicarbonate for metabolic acidosis, and naloxone on the advice of the National Poisons Information Service (NPIS). After approximately 1 h, return of spontaneous circulation (ROSC) was achieved. He required significant inotropic and vasopressor support, and there was a large ventilatory shunt.

A CT scan immediately after ROSC showed imminent cerebral herniation, for which neurosurgical advice was obtained. He was commenced on haemodiafiltration to control his metabolic acidosis, and active warming was commenced to try to achieve normothermia. His inotrope requirements continued to escalate, so, on the advice of NPIS, a standard dose of intralipid was given, with significant improvement in his cardiovascular and respiratory failure. To maintain a mean arterial pressure (MAP) of 90 mmHg, the noradrenaline requirement fell from 1.48 to 1.04 mcg/kg/min, an improvement of 30%, and the adrenaline requirement from 0.78 to 0.56 mcg/kg/min (28%) within a few minutes, and this improvement lasted for approximately 1 h. The alveolar-arterial oxygen difference fell from 77.3 to 64.8 kPa, an improvement of 16%, within a few minutes of the lipid emulsion. However, his cardiorespiratory function subsequently deteriorated again, and after discussion with his family, active treatment was withdrawn. He died 12 h after the initial ROSC.

Urine toxicology subsequently was negative for the compounds analysed, with the exception of codeine,

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which the patient had taken a standard dose just prior to admission.

Discussion

Biology of Kratom

Kratom (*Mitragyna speciosa*) a tree indigenous to Southeast Asia, especially in the central and southern parts of Thailand. It was first described by the Dutch botanist Pieter Korthals in 1839, so named because the stigmas were thought to resemble the shape of a bishop's mitre. The tree can grow to a height of 15 m. It is evergreen and produces yellow flowers. Mitragyna trees are used for their fine timber, as well as in traditional medicine and, more recently, as a recreational drug.

The leaves are reported to be more potent in the autumn. The leaves are usually chewed, or made into a paste or tar for consumption. Kratom may also be smoked.

Pharmacology of Kratom

Kratom (Mitragyna Speciosa) contains a large variety of pharmacoactive alkaloids, acting on a number of receptors; at least 25 have now been isolated.[1] Of these, Mitragynine is the commonest, accounting for 66% of the content of the extracted alkaloid.[1] Although occurring in a much smaller amount (2%),[1] another compound, 7-hydroxymitragynine, may be more biologically active. Mitragynine and 7-hydroxymitragynine are both opioid agonists, acting on supraspinal mu- and delta- opioid receptors.[2] Mitragynine is also an adrenergic receptor agonist. At least two alkaloid extracts appear to have calcium channel blocking action[1]; other compounds have activity at NMDA and 5-HT2A receptors.[1] Mitragynine also interferes with function of the neuromuscular junction, producing skeletal muscle relaxation.[3]

Mitrgynine has a long duration of action, with a terminal half-life of 23.24 h and a very high volume of distribution.[4] Mitragynine is a lipophilic alkaloid and is poorly soluble in water.[5]

As a result, it is a stimulant at low doses; at higher doses, it produces a sensation of euphoria. A wide range of other effects are proported, including antibacterial, antimalarial, antileukaemic, antipyretic and diuretic effects.

Treatment of Kratom toxicity

Most internet sites report the benign nature of Kratom. It is very rare to need treatment. It is often cut with other compounds, which may be responsible for the side effects.

Death from Kratom appears to be very rare, but has been reported.[6] Most internet sites report its safety. It has, however, recently become banned in the UK under the Psychoactive Substances Act.

The cardiorespiratory arrest was considered by the clinical team and subsequently by HM Coroner to be a direct result of the Kratom ingestion, and treatment was mainly supportive. Extracorporeal membrane oxygenation (ECMO) was considered, but given the developing multi-organ failure, was not considered to be appropriate. Naloxone was suggested by National Poisons Information Service (NPIS), but had no discernible response.

On the advice of NPIS, a standard dose of Intralipid was tried with good effect. The dose of inopressor was able to be reduced by 30%, and there was significant improvement in oxygenation and ventilation. We postulate that a proportion of the cardiovascular collapse was therefore a result of cardiotoxicity of the Kratom. We postulate that at least a proportion of the compounds are cardiotoxic. Lipid emulsion therapy might be expected to have a positive effect, since at least some compounds are lipophilic,[5] and that some of the compounds have calcium channel blocking (CCB) activity.[1]

The improvement lasted for approximately 1 h, followed by a further deterioration. A further dose was considered, but given the catastrophic brain injury and the deterioration in other organ function, it was considered futile.

Given the cardiotoxicity of the compounds, and the CCB effects, high-dose insulin might also be considered to be beneficial.

The use of intralipid

Interest in the use of lipid emulsion has grown since a chance observation almost 20 years ago that lipid emulsion increased the dose of bupivacaine required to produce asystole in rats.[7] Measurement of the partitioning suggested that the local anaesthetic (LA) partitioned into the lipid,[7] and is now recommended treatment for LA toxicity, including in refractory cardiac arrest.[8] There are reports of its success in wide range of drugs, including calcium channel blockers, beta blockers, typical and atypical antipsychotics, and tricyclic and other antidepressants, whose one common feature would appear to be that they are all lipophilic.

The mechanism of action is not clear. Possible mechanisms include lipid sink, improving cardiac fatty acid metabolism, changes in sodium channel function, changes in calcium flux, or cardioprotection from cell damage.[9]

The optimum dose is not clear. Current guidelines advise 1.5 ml/kg as an initial bolus, followed by 0.25 ml/kg/min over 30–60 min, or 9–17.5 ml/kg[10] but larger doses are usually well tolerated. In one reported case, there were no cardiorespiratory complications in a patient who received 2 L of 20% lipid emulsion in error, during treatment for an amlodipine

overdose.[11] Even this dose is probably well within safe limits; rat studies suggest that that median lethal dose is 68 ml/kg.[12]

However, while undoubtedly of benefit in some cases, there is reported concern over publication bias, and the lack of a clear mechanism of action or optimal dose. Intralipid is often given simultaneously with other treatments, making its efficacy difficult to determine. While often reported to be benign, there are emerging reports of side effects. In one review of nine patients treated with lipid emulsion for drug toxicity, six developed complications that were thought to be associated with the lipid infusion. Two patients developed pancreatitis, and four patients developed lipaemia sufficient to interfere with interpretation of laboratory studies. Three patients developed acute respiratory distress syndrome (ARDS)[13] associated with the lipid infusion.

Conclusion

Kratom is widely reported to be benign. We present here a possible case of Kratom toxicity resulting in cardiorespiratory arrest, in the absence of other identified causes.

We wish to highlight that the effects may not be as benign as are frequently reported. It contains multiple compounds acting on different receptors, including on calcium channels. Significant cardiorespiratory improvement in this case suggests that lipid emulsion therapy may be of benefit. Given the calcium channel blockade, we postulate that high dose insulin may also be of benefit, in addition to standard supportive care.

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Patient consent

Written consent from next of kin obtained. Written permission was obtained from HM Coroner for Surrey to publish.

Disclaimer

This article is not intended as a definitive guide to management.

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