ELMER PRESS

Case Report

Int J Clin Pediatr. 2018;7(4):55-58

Neonatal Withdrawal Following in Utero Exposure to Kratom

Emma Nellhaus[a], Lacey Andrews[a], Jessica Haas[b], David Miskell[b], Kenneth Kurek[b], Zachary Hansen[c], Todd H. Davies[a, d]

Abstract

In recent years, the clinical definition of neonatal abstinence syndrome (NAS) has been expanded to describe neonates experiencing withdrawal due to *in utero* exposure to numerous neuroactive substances, not exclusively opioids. Complex NAS cases involving exposure to multiple and unusual narcotics have become widespread. Kratom is one such substance. It is extracted from tropical tree leaves, and can be used both as a recreational drug and to mitigate opioid withdrawal. Although kratom may potentially serve as a viable opioid alternative, its activity and the consequences of controlled use are largely unstudied, particularly in the pregnant population. A newborn male infant was not initially identified as being at risk for withdrawal due to no maternal admission of substance use and maternal urine drug screen was negative. On the first day of life (DOL), the neonate was observed to exhibit significant signs of withdrawal including high-pitched crying, facial grimacing, irregular respiratory pattern, mottling, and mild undisturbed tremors. Upon interview with the mother it was noted that there was heavy caffeine use, daily cigarette smoking, daily use of the "herbal alternative" (kratom) throughout the pregnancy. In this report, we present a case of NAS precipitated by *in utero* exposure to kratom, discuss the present body of research regarding kratom and consider potential implications of escalating kratom use on the incidence and severity of NAS. For this prenatally exposed neonate, clonidine was successfully used to control withdrawal symptoms.

Keywords: NAS; Neonate; Withdrawal; Kratom

Introduction

Neonatal abstinence syndrome (NAS) is a withdrawal syndrome observed in neonates after exposure to drugs *in utero*. This syndrome has been seen with a variety of neuroactive substances, but is typically associated with *in utero* exposure to opioids. Many of the neonates in the southwestern region of West Virginia born with NAS are treated at Cabell Huntington Hospital. Our institution is faced with increasingly complex, novel withdrawal profiles in neonates prenatally exposed to multiple or unusual substances. These complicated withdrawal profiles can be partially attributed to neuroactive substances in the area, such as kratom. This report is the first verifiable case of kratom exposure in our institution. Kratom is a plant-derived substance that can cause a stimulant effect, which may increase energy levels and help combat fatigue when used in low doses [1]. When used in higher doses, kratom has been shown to mimic the analgesic and sedative effects of opioids [1]. When used regularly, much like substances that act on opioid receptors, dependence to kratom can develop, resulting in withdrawal after cessation of use [1, 2]. Recently in Huntington, West Virginia, there has been an increase of kratom. We have identified the first verifiable case of neonatal withdrawal after prenatal exposure to kratom at out our institution.

Case Report

A male infant was born by vaginal birth at 39 weeks gestation to a 33-year-old gravida 6, para 2 Caucasian female. The birth weight was 3,375 g, birth length was 50.8 cm, head circumference was 34 cm, and 1 and 5-minute Apgar scores were both 9. A post birth physical exam and neurological exam was typical: temperature 36.7 °C, heart rate 140 bpm, respiratory rate 66/min with no visible detectable deficits or deformities outside the withdrawal symptoms described below. All lab values were within the adequate ranges. The birth was uncomplicated apart from the presence of light meconium.

The neonate was not initially identified as being at risk for withdrawal as there was no maternal admission of substance use and maternal urine drug screen was negative. On the first day of life (DOL), the neonate was observed to exhibit significant signs of withdrawal including high-pitched crying, facial grimacing, irregular respiratory pattern, mottling, and mild undisturbed tremors. Consequently, the neonate was transferred from the Newborn Nursery to our Neonatal Therapeutic Unit (NTU), which provides specialized care for babies in need of treatment for withdrawal.

The mother was a 34-year-old non-Hispanic white female with some college who attended all prescribed prenatal visits. She denied alcohol consumption or drug use other than what is

Manuscript submitted September 11, 2018, accepted September 25, 2018

[a]Department of Family and Community Health, Joan C Edwards School of Medicine at Marshall University, Huntington, WV 25701, USA
[b]Hoops Family Children's Hospital at Cabell Huntington Hospital, Huntington, WV 25701, USA
[c]Department of Family Medicine, Valley Health Systems, Huntington, WV 25701, USA
[d]Corresponding Author: Todd H. Davies, Department of Family and Community Health, Joan C Edwards School of Medicine at Marshall University, 1600 Medical Center Drive, Huntington, WV 25701, USA.
Email: daviest@marshall.edu

doi: https://doi.org/10.14740/ijcp317w

Figure 1. Kratom capsules.

reported in this report. Urine drug screens were negative. Maternal labs were negative for hepatitis C, human immunodeficiency virus (HIV) and syphilis. There was no past history of hypertension, diabetes or thyroid deficiencies. Upon interview with the mother it was noted that there was heavy caffeine use and daily cigarette smoking throughout the pregnancy, although reported cigarette use was reduced from 0.5 pack per day to 0.2 pack per day by the second trimester. Daily medications included prenatal vitamins, iron supplements, and zolpidem (Ambien) 10 mg *quarter in die* (QID). In an accident 3 years prior, the mother suffered a herniated disc and had been receiving hydrocodone bitartrate/acetaminophen tablets (Vicodin) for pain control. She reported that after becoming pregnant, the pain clinic she had been attending discontinued her prescription and advised her to switch to buprenorphine for pain control. She declined treatment with buprenorphine and stated that she instead opted for an "herbal alternative" to medication-assisted treatment that reportedly controls her cravings and withdrawal symptoms, kratom. In the first trimester of her pregnancy she took kratom (*Mitragyna speciosa)* capsules, shown in Figure 1, of an unknown amount and concentration three times daily and decreased her use of kratom throughout the rest of her pregnancy to as needed. Exposure continued throughout the pregnancy, but actual amounts could not be verified.

After transfer to the NTU, the neonate's Finnegan scores quickly escalated. The withdrawal symptoms were predominantly neurological in nature, with mild undisturbed and moderate disturbed tremors. The umbilical cord toxicology report results were negative for all substances. The cord toxicology did not validate exposure to kratom, but did suggest that there was no evidence of concomitant use of opioids later in the pregnancy. Standard umbilical toxicology testing does not include kratom. Non-pharmacological interventions including swaddling, minimal stimulation, and skin-to-skin contact were unsuccessful in controlling withdrawal symptoms, and clonidine was started on DOL 2. This temporarily reduced withdrawal symptoms. On DOL 4, neurological symptoms worsened as the baby exhibited severe undisturbed tremors, hyperactive Moro reflex, and increased muscle tone. Consequently, the clonidine dose was increased and ranitidine and Mylicon were added for relief of gastroesophageal reflux and gas, respectively. The remainder of the hospital stay was unremarkable. A clonidine wean was begun on DOL 6 and the neonate was discharged home with the mother on DOL 10 with no further pharmacological treatment.

The patient was transitioned from breast milk to "sensitive" formula on DOL 2 and regained birth weight by DOL6 despite the increasing neurologic symptoms. Growth continued to an overall increase of 125 g in weight and 0.2 inches in length. By 5 months of age, the patient was not able to fully support his head, but had no other detectable delays.

Discussion

Here we described a case of a newborn with demonstrating post-natal opioid withdrawal with exposure to kratom and no opioid exposure. There is a lack of clearly reported cases of kratom-induced withdrawal in prenatally-exposed neonates despite increased use of the herbal remedy. This underreporting is likely due to very few institutions having the ability to determine kratom use by toxicology. We also report the successful use of clonidine and palliative care to treat the neonate. There is still much to understand about how kratom might affect the developing neonate.

Mitragyna speciosa, commonly known as kratom, is a naturally derived opioid-like analgesic that can be chewed, smoked, or ingested [3, 4]. The leaves of *Mitragyna speciosa* contain biologically active alkaloids such as mitragynine, paynantheine, speciogynine, 7-hydroxymitagynine, speciophylline, and 20 other alkaloids found only in trace amounts [4, 5]. Kratom's opioid-like characteristics can primarily be attributed to the alkaloid constituents: mitragynine and 7-hydrosymitagynine [4]. Mitragynine comprises 66% of the total alkaloid content, while 7-hydrosymitagynine only comprises 7% of the total alkaloid content [4, 5]. However, 7-hydrosymitagynine is 46-fold more potent than mitragynine and 13-fold stronger than morphine as an antinociceptive compound [5]. Individual alkaloid concentration can vary among kratom products, as studies of several commercial kratom products have revealed 7-hydroxymitragynine concentrations that are considerably higher than what would be observed in fresh or dried *M. speciosa* levels [6]. Concentration of the alkaloid components vary among different species of kratom, depending on the geographic location, plant age, and the specific blend of plant parts that comprise various supplies of plant material [7].

The kratom alkaloids have a wide range of pharmacological effects on various nerve pathways, including opioid receptor agonism and antagonism, calcium channel blocking, alpha-2 antagonism, and serotonin depletion. These alkaloid components are associated with analgesia, antitussive effects, smooth muscle relaxation, vasodilation, anti-inflammatory, and antipyretic effects [8]. By stimulating alpha-2 adrenergic receptors, kratom can mimic drugs such as clonidine to man-

age pain, anxiety, and symptoms of withdrawal [4, 9]. However, the combined physiological effects of these alkaloids are not fully understood.

The opioid-like effects of kratom come from its major alkaloids, mitragynine, 7-hydroxymitragynine, and its oxidative metabolite mitragynine pseudoindoxyl; which either partially agonizes mu-opioid receptors or competitively inhibits kappa- and delta-opioid receptors. Adrenergic blocking and calcium channel antagonism effects are minor and come primarily from alkaloids that each comprises less than 1% of total kratom alkaloids typically found in any given sample [7, 10]. Like morphine and other classical opioids, the mechanism of opioid receptor action of mitragynine is through binding to guanine nucleotide-binding proteins (G proteins) that act as molecular switches that stimulate nociception by regulating conversion of guanosine triphosphate to guanosine diphosphate through a complex cellular pathway. However, mitragynine and other major kratom alkaloids bind to sites on G proteins differently than morphine [11]. These findings have prompted new research into these compounds as potential novel analgesics that may lack the drawbacks exhibited by classical opioids, such as tolerance and dependence [10]). However, there is no established understand of appropriate therapeutic or toxic dosages. Other major kratom alkaloids such as paynantheine, speciogynine, and speciociliatine antagonize opioid receptors are being studied as novel antidepressants [10, 11]. These mechanisms may elucidate why kratom attenuates withdrawal from opiates, benzodiazepines, alcohol, and tobacco. Despite this, these mechanisms may also suggest danger of kratom use when used concomitantly with other substances. For example, in animal studies, caffeine co-administration enhanced the effects of kratom alkaloids. Co-administration of acetaminophen also enhanced the effects of kratom in the same animal models [5]. In addition, co-administration of caffeine and nicotine may have attributed to a more severe withdrawal profile in this case.

News of kratom has spawned public interest from persons seeking natural products for pain management, recreational purposes, substitution of illicit opioids, or to relieve symptoms from opioid withdrawal [5, 12]. Kratom can be purchased online, from head shops, and some health food stores. Kratom is taken orally and is produced as powders, leaves, extracts, and capsule formulations in prices ranging between $8.00 and $21.00 per ounce. Reported dosages vary widely, from 1 g up to 50 g, depending on which product is being used. Onset of effect as reported by end users is described to be between 15 min and 4 h with average durations of 2 to 5 h. Data regarding dosage or pharmacokinetic information presented above comes from lay, ungoverned sources such as blogs, online kratom stores, and private websites supported by kratom users.

Several case reports describing adult patients with kratom dependence and consequential withdrawal currently exist in the literature [13-15]. In these reports, the patients exhibited tolerance to the effects of kratom and withdrawal symptoms when use is discontinued. Similar to opioids, kratom withdrawal can begin from 6 to 24 h after the last dose. The majority of the literature suggests that withdrawal from kratom in adult patients is of quick, severe onset and has been shown to subside in approximately 1 week's time. Notably, the withdrawal symptoms are more closely related to clonidine withdrawal rather than that of opioid withdrawal, characterized by irritability, dysphoria, nausea, diarrhea, hypertension, insomnia, rhinorrhea, myalgia, and arthralgia [4]. In addition to withdrawal, reported side effects of kratom use include tachycardia, hypertension, nausea, constipation, confusion, hallucinations, seizures, and sedation [2, 4, 14]. Prolonged use of high doses (more than 100 mg/kg) of kratom has been connected to drug induced hepatotoxicity, but there are only a handful of reports and causation has yet to be confirmed [16, 17]. Although adverse events associated with opioids can be managed with naloxone, there are non-opioid mechanisms involved in kratom withdrawal that may suggest superiority of non-opioid antagonist treatment options or the use of those options in adjunctively to treat kratom adverse events [12, 18].

The clinical description associated with withdrawal from kratom in adult patients was comparable to that which we saw in this case. The neonate's withdrawal exhibited an acute onset, with a more abrupt increase in severity of symptoms typically only seen in opioid exposures. This case was distinctive in that it was our first confirmed kratom NAS patient and was not complicated by polysubstance exposure. Despite maternal use of caffeine, cigarettes, and zolpidem during the pregnancy, the reported clinical consequences of these do not explain the withdrawal that was observed in the neonate [19-21]. Maternal report and negative urine drug screen also suggest that opioids were not used throughout the pregnancy.

The NTU cares for neonates suffering from withdrawal by treating them in a therapeutic environment with minimal noise and low lighting and administers supportive care such as swaddling and therapeutic handling. If these interventions are unsuccessful in controlling withdrawal symptoms, pharmacological intervention is initiated. Withdrawal signs and symptoms are documented and scored through the Finnegan Scoring System, which indicates the severity of NAS [22]. Our case argues the theory that kratom withdrawal may be better managed through therapies that differ from those given to opioid-exposed neonates, as evidenced by the successful control of withdrawal symptoms in this newborn patient with clonidine.

Conclusions

Although preliminary research suggests there is promise in kratom's capacity as an opioid replacement therapy [12], long-term consequences in adults using kratom are not well understood, as the literature is still lacking in thorough, controlled clinical investigation. Regardless of the clinical potential of kratom, outcomes for pregnant women and their neonates who are prenatally exposed to kratom are even less explored and comprehended. To the best of our knowledge, very few case reports exist describing and treatment of neonatal withdrawal from kratom due to *in utero* exposure.

Funding Support

No honorarium or grant or other form of payment was given to

anyone to produce the manuscript.

Conflict of Interest

The authors have no COI to disclose.

Financial Disclosure

The authors have no financial relationships relevant to this article to disclose.

Abbreviations

NAS: neonatal abstinence syndrome; NTU: neonatal therapeutic unit; QID: *quarter in die* (four times per day); DOL: day of life

References

1. Centers AA. Kratom withdrawal, detox, and tapering. 2018. Available from: https://americanaddictioncenters.org/withdrawal-timelines-treatments/kratom/.
2. Anwar M, Law R, Schier J. Notes from the field: Kratom (Mitragyna speciosa) exposures reported to Poison Centers - United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65(29):748-749.
3. Maclaren E. The Effects of kratom use. 2018. Available from: https://drugabuse.com/library/the-effects-of-kratom-use/.
4. Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J Am Osteopath Assoc. 2012;112(12):792-799.
5. Hassan Z, Muzaimi M, Navaratnam V, Yusoff NH, Suhaimi FW, Vadivelu R, Vicknasingam BK, et al. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. Neurosci Biobehav Rev. 2013;37(2):138-151.
6. Ward J, Rosenbaum C, Hernon C, McCurdy CR, Boyer EW. Herbal medicines for the management of opioid addiction: safe and effective alternatives to conventional pharmacotherapy? CNS Drugs. 2011;25(12):999-1007.
7. Kruegel AC, Gassaway MM, Kapoor A, Varadi A, Majumdar S, Filizola M, Javitch JA, et al. Synthetic and receptor signaling explorations of the mitragyna alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. J Am Chem Soc. 2016;138(21):6754-6764.
8. Takayama H. Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, Mitragyna speciosa. Chem Pharm Bull (Tokyo). 2004;52(8):916-928.
9. Giovannitti JA, Jr., Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog. 2015;62(1):31-39.
10. Takayama H, Ishikawa H, Kurihara M, Kitajima M, Aimi N, Ponglux D, Koyama F, et al. Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. J Med Chem. 2002;45(9):1949-1956.
11. Hurowitz EH, Melnyk JM, Chen YJ, Kouros-Mehr H, Simon MI, Shizuya H. Genomic characterization of the human heterotrimeric G protein alpha, beta, and gamma subunit genes. DNA Res. 2000;7(2):111-120.
12. White CM. Pharmacologic and clinical assessment of kratom. Am J Health Syst Pharm. 2018;75(5):261-267.
13. Diep J, Chin DT, Gupta S, Syed F, Xiong M, Cheng J. Kratom, an emerging drug of abuse: a case report of overdose and management of withdrawal. A A Pract. 2018;10(8):192-194.
14. Boyer EW, Babu KM, Macalino GE. Self-treatment of opioid withdrawal with a dietary supplement, Kratom. Am J Addict. 2007;16(5):352-356.
15. McWhirter L, Morris S. A case report of inpatient detoxification after kratom (Mitragyna speciosa) dependence. Eur Addict Res. 2010;16(4):229-231.
16. Pantano F, Tittarelli R, Mannocchi G, Zaami S, Ricci S, Giorgetti R, Terranova D, et al. Hepatotoxicity Induced by "the 3Ks": Kava, Kratom and Khat. Int J Mol Sci. 2016;17(4):580.
17. Kapp FG, Maurer HH, Auwarter V, Winkelmann M, Hermanns-Clausen M. Intrahepatic cholestasis following abuse of powdered kratom (Mitragyna speciosa). J Med Toxicol. 2011;7(3):227-231.
18. Nelsen JL, Lapoint J, Hodgman MJ, Aldous KM. Seizure and coma following Kratom (Mitragynina speciosa Korth) exposure. J Med Toxicol. 2010;6(4):424-426.
19. Greenwood DC, Thatcher NJ, Ye J, Garrard L, Keogh G, King LG, Cade JE. Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis. Eur J Epidemiol. 2014;29(10):725-734.
20. Mei-Dan E, Walfisch A, Weisz B, Hallak M, Brown R, Shrim A. The unborn smoker: association between smoking during pregnancy and adverse perinatal outcomes. J Perinat Med. 2015;43(5):553-558.
21. Wikner BN, Stiller CO, Bergman U, Asker C, Kallen B. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidemiol Drug Saf. 2007;16(11):1203-1210.
22. Finnegan LP, Connaughton JF, Jr., Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis. 1975;2(1-2):141-158.

