HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

OBSERVATIONS IN HEPATOTOXICITY

Cholestatic Hepatitis From Prolonged Kratom Use: A Case Report

Christina Dorman,[1] Mark Wong,[2] and Aazib Khan[3]

Kratom is an herbal product made from the leaves of Southeast Asian *Mitragyna* trees. The leaves can be chewed or an extract made and used as a powder or tablets. Kratom is used by local people to relieve fatigue and muscle aches and manage pain, diarrhea, or opioid withdrawal.[1] The effects of kratom appear to be dose dependent, in that low doses tend to increase alertness whereas higher doses sedate. The active components of kratom are natural alkaloids, mitragynine, and 7-hydroxymitragynine (7-OHMG), which act on mu, delta, and kappa opioid receptors. 7-OHMG has been reported to have 13-fold higher potency than morphine.[1] Kratom has been increasingly used in Western countries and the United States to counteract fatigue and anxiety and relieve opioid withdrawal symptoms.[2] Literature reports of toxicity are rare, but are increasing in number. This case report describes intrahepatic cholestasis arising after intake of maeng da kratom, the Malay term used for extract derived from *Mitragyna speciosa*.

Case Report

A 58-year-old Caucasian man with schizoaffective disorder was admitted to the hospital for jaundice and liver injury suspected to be resulting from kratom use. One year previously (September 2013), he had ingested kratom powder (1 tablespoon daily) for 3 months to relieve anxiety and aid in relaxation. At that point, his psychiatrist noticed jaundice and ordered laboratory tests, which showed liver abnormalities (Table 1) that gradually improved after discontinuation of kratom. During this period, his psychotropic medications were initially held for 1 week and then reintroduced without recurrence of the liver test abnormalities. The kratom product used was distributed by Experience Alternatives Inc., and the product label listed its ingredient as "pure maeng da kratom leaf," describing the herbal powder as "100% effective and 100% natural." The patient obtained bulk packages of the product from a novelty store.

One month before the subsequent episode of jaundice, he again started taking kratom powder daily. He stopped the product when he first noticed dark urine and sought medical help when obvious jaundice arose a few days later. He denied fever, rash, or pruritus. His other medications included quetiapine (100 mg daily) and sertraline (50 mg daily), both of which he had taken at these doses for more than 2 years except for the short period mentioned previously. He denied taking other herbals, dietary supplements, or drugs of abuse or drinking excessive alcohol. Physical examination showed normal vital signs. His body mass index was 24.5 kg/m^2. He had mild confusion, but no evidence of edema or ascites. Laboratory tests showed a total bilirubin of 25.6 mg/dL (direct, 17.1), alanine aminotransferase (ALT) 106 U/L, aspartate aminotransferase (AST) 49 U/L, and alkaline phosphatase (ALP) 790 U/L (R ratio = 0.24, indicating cholestatic injury). The international normalized ratio (INR) was normal, but ammonia levels were raised at 161 μmol/L (normal, <47). Serum salicylate and acetaminophen levels were not detectable. Tests for hepatitis A, B, and C were negative as were antinuclear and smooth muscle antibodies. Abdominal ultrasound showed irregular hepatic texture, but no evidence of biliary obstruction. A liver biopsy was not performed.

The patient appeared stable overall and he was discharged 2 days later, at which time liver tests were improving and psychotropic medications were resumed. He did not return in follow-up to document eventual normalization of liver tests.

Discussion

Kratom is a psychoactive botanical product whose major effects are believed to be mediated by its natural alkaloids (mitragynine and its metabolites), which

Abbreviations: 7-OHMG, 7-hydroxymitragynine; ALP, alkaline phosphatase; ALT, alanine aminotransferase; INR, international normalized ratio.

Received August 14, 2014; accepted November 14, 2014.

Address reprint requests to: Christina Dorman, B.S., 4114 Medical Drive, Apt. 19205, San Antonio, TX 78229. E-mail: christina.b.dorman@gmail.com.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.27612
Potential conflict of interest: Nothing to report.

Table 1. Laboratory Values at the Time of the First and Second Episodes of Jaundice

		Laboratory Test				
Exposure/date		**ALT (U/L)**	**ALP (U/L)**	**Bilirubin (mg/dL)**	**INR**	**Comment**
Preexposure		**25**	**149**	**0.7**	**1.0**	**Routine Testing**
First instance	September 2013	79	270	9.7		Kratom stopped
	October 2013	45	263	2.3	0.9	
	December 2013	43	201	0.5		
Second instance	July 2014	106	790	25.6	1.1	Admission
	36 hours later	93	730	20.8	1.0	Discharge
Normal values		17-63	42-113	0.3-1.1	<1.2	

appear to have intrinsic opioid receptor agonist activity. Serious adverse events associated with kratom use have been linked largely to this opioid activity and include confusion, stupor, coma, and respiratory arrest. These adverse events appear to be dose related and direct "on-target" effects. In addition, kratom has been linked here and in at least one other report to cholestatic liver injury. The injury appears to be idiosyncratic, but its association with kratom is convincing. The case reported here is made most convincing by the previous history of jaundice while taking kratom, which reversed upon withdrawal and recurred with restarting the same kratom preparation with a shortened latency (1 vs. 2 months). Other causes of cholestatic injury were excluded. Kratom is a botanical product with more than 35 known chemical ingredients. The constituents responsible for the idiosyncratic liver injury may not be the same as those responsible for its psychological effects.

Kratom use has been increasing in Western countries, including the United States, where it is advertised over the Internet and in supplement stores as a sedative with euphoric effects. Of interest, kratom has been used for centuries in Southeast Asia, but has been reported to cause liver injury only in Western countries. A similar discordancy exists for other traditional herbal medications, such as kava, khat, noni juice, and black cohosh, suggesting that the liver injury may be the result of a contaminant or error in identification or preparation of the herbal product. Nevertheless, this report reinforces the need to query carefully for possible herbal and over-the-counter medication use in any patient presenting with liver injury of unknown cause.

Christina Dorman, B.S.[1]
Mark Wong, Pharm.D.[2]
Aazib Khan, M.D.[3]
[1]*University of Texas at Austin College of Pharmacy*
University of Texas Health Science Center San Antonio
San Antonio, TX
[2]*Audie L. Murphy VA Hospital*
South Texas Veterans Health Care System
University of Texas at Austin College of Pharmacy
University of Texas Health Science Center San Antonio
San Antonio, TX
[3]*Internal Medicine*
University of Texas Health Science Center San Antonio
San Antonio, TX

References

1. 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;112:792-799.
2. Forrester M. Kratom exposures reported to Texas poison centers. J Addict Dis 2013;32:396-400.
3. Kapp F, Maurer H, Auwärter V, Winkelmann M, Hermanns-Clausen M. Intrahepatic cholestasis following abuse of powdered kratom (*Mitragyna speciosa*). J Med Toxicol 2011;7:227-231.
4. SNI National. SNI National is voluntarily recalling Kratom XL 4 pack, Maeng Da Kratom 10 pack, Max Kratom 20 pack, and Bali Kratom 40 pack due to undeclared drug ingredients. 2014. Available at: http://www.fda.gov/Safety/Recalls/ucm389350.htm. Accessed August 1, 2014.