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Liver Injury Associated with Kratom, A Popular Opioid-Like Product: Experience from the U.S. Drug Induced liver Injury Network

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Drug-Induced Liver Injury Network

Abstract

Background—Kratom is a botanical product used as an opium substitute with abuse potential.

Methods—Assessment of suspected cases of kratom-induced liver injury in a prospective US cohort.

Results—Eleven cases of liver injury attributed to kratom were identified with a recent increase. The majority were male with median age 40 years. All were symptomatic and developed jaundice

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with a median latency of 14 days. The liver injury pattern was variable, most required hospitalization and all eventually recovered. Biochemical analysis revealed active kratom ingredients.

Conclusion—Kratom can cause severe liver injury with jaundice.

Keywords

Kratom; hepatotoxicity; mitragynine; 7-hydroxymitragynine; opioid

Background

Kratom is a botanical product extracted from the tropical evergreen tree, *Mitragyna speciosa,* taken as a tea or chewable leaves (1). Low dose kratom has stimulant effects, but a sedative narcotic effect at higher doses with many adverse events reported (2). Kratom's most important components, mitragynine and 7-hydroxymitragynine, have psychoactive effects acting as μ-opioid receptor agonists (1). Kratom is readily available online and in herbal medicine it is used as an opium substitute to reduce withdrawal symptoms (3). The National Poison Data System reported 1800 cases of kratom poisoning from 2011–2017, with two thirds occurring in 2016–2017 (4).

The U.S. Drug-Induced Liver Injury Network (DILIN) has prospectively enrolled cases of liver injury due to drugs and herbal and dietary supplements (HDS) since 2003 (5). Patients with suspected DILI undergo testing to exclude alternative causes of liver injury and expert opinion determines whether the liver injury is due to a drug or HDS. The aim of this study is to describe the DILIN's experience with kratom-induced liver injury. Available kratom products were analyzed at the National Center for Natural Products Research (NCNPR) at the University of Mississippi for the presence of mitragynine and 7-hydroxymitragynine.

Methods

Suspected cases of DILI within 6 months of injury onset meeting predefined laboratory criteria are prospectively enrolled in DILIN. Eligibility criteria include total bilirubin ≥2.5 mg/dL or INR >1.5 *and* any elevation in alanine or aspartate aminotransferase (ALT or AST) or alkaline phosphatase (AlkP) levels; *or* elevations of ALT or AST above 5 times the upper limit of normal (ULN) or AlkP above 2 times ULN on 2 consecutive measurements at least 24 hours apart. All non-drug or non-HDS causes for liver injury are excluded.

A standardized protocol assesses the relationship between the use of a medication or HDS and liver injury (6). Causality is graded by expert consensus opinion as either definite (>95% likelihood), highly likely (75–95%), probable (50–74%), possible (25–49%) or unlikely (<25%).

In HDS suspected cases, available product is analyzed at the NCNPR to verify the product label, and to search for common hepatotoxins. High resolution HLA Class I and II gene sequencing on whole blood DNA is performed in the Vanderbilt University Medical Center Immunogenomics, Microbial Genetics and Single Cell Technologies core.

Results

Between 2003 and 2019, 404 cases of liver injury associated with HDS were enrolled into DILIN. Of these, 11 cases with definite, highly likely or probable causality were attributed to kratom (table 1). Cases occurred infrequently until 2019, when 4 cases were enrolled (Figure 1). Of the 11 cases, 9 were male, median age was 40 years with a median 14 days of kratom use prior to DILI onset. The median latency before symptom onset was 14 days and laboratory abnormalities was 21 days. One patient was abusing alcohol (3 had a remote history of heavy use) and kratom was used for several reasons. At presentation, all were symptomatic. Ten patients had an initial bilirubin greater than 2.5mg/dL and all 11 developed jaundice (median peak total bilirubin 11.7 mg/dL). The initial median serum ALT was 362 U/L and median AlkP 255 U/L with 6 of 11 having a mixed pattern of liver injury (R value 2–5). Autoimmune serology was negative. Eight patients were hospitalized and 3 developed an elevated INR, with no fatalities. Ten patients recovered completely by 6 months and most had a rapid improvement. One patient had mildly elevated liver biochemical tests that normalized at 1 year.

Biochemical analysis of 3 products revealed the presence of mitragynine and 7-hydroxymitragynine with no other pharmaceutical adulterants, toxicants, or contaminants. Genetic analysis revealed that one patient carried the minor allele (A nucleotide) of the PTPN22 SNP rs2476601. Seven of eight European Americans had either HLA-B*57:01 or HLA-B*44:03 alleles; both had the same allele frequencies (AF=0.25), but higher than their corresponding AF in the general population (AF=0.04 and 0.05). In total, four patients carried one HLA-B*57:01 allele, and three patients carried HLA-B*44:01 but one had homozygous HLA-B*44:03.

Discussion:

Between 2004–2019, 2193 cases of suspected DILI were enrolled in the prospective DILIN registry with 1950 adjudicated for causality. Among those adjudicated, 369 (19%) were attributed to HDS. Thus, these 11 cases of kratom associated liver injury represents approximately 3% of cases of HDS related liver injury and 1% of cases overall. Importantly, only 3 cases were enrolled during the first 10 years, with 8 enrolled in the last 3 years. The increasing use of kratom is illustrated by increasing reports of related toxicity and deaths, partially because of its purported effects in ameliorating opioid withdrawal (2). The typical patient was a healthy male presenting with jaundice, itching and a mixed or cholestatic pattern of injury. The latency to onset was invariably short, ranging from 5–28 days. Immunoallergic and autoimmune features were not prominent. All 11 patients recovered with no evidence of chronic injury although several cases were severe and associated with significant hepatic dysfunction.

Although no patient died from liver failure in this series, kratom use can be fatal with the Centers for Disease Control reporting 90 kratom-related deaths due to respiratory depression and coma (2). Because of the lack of pharmacological data on kratom, the FDA evaluated a biologic simulation model of the product’s constituents and noted structural similarities

between kratom and opioids with several ingredients predicted to bind to μ-opioid receptors and to behave as opioid agonists (7).

To date, 6 reports of Kratom associated liver injury have been published with a recent review of 26 cases that were 65% male with a median age of 32 years (8). The common presentations were abdominal discomfort, jaundice and other cholestatic symptoms, with median latency to onset of 22 days and cholestasis commonly seen on liver biopsy.

The small sample size limited the genetic analysis. HLA B*57:01 and B*44:03 had a higher allelic frequency than the general population and 10 of 11 patients were homozygous for the PTPN22 G allele (9, 10). Only 1 patient had HLA*B35:01 that has been linked to other forms of HDS DILI (11).

In summary, kratom is readily available and, using the DILIN as a bellwether for use in the population, may be an increasingly frequent cause of DILI. Practitioners should be aware of the risk of severe liver injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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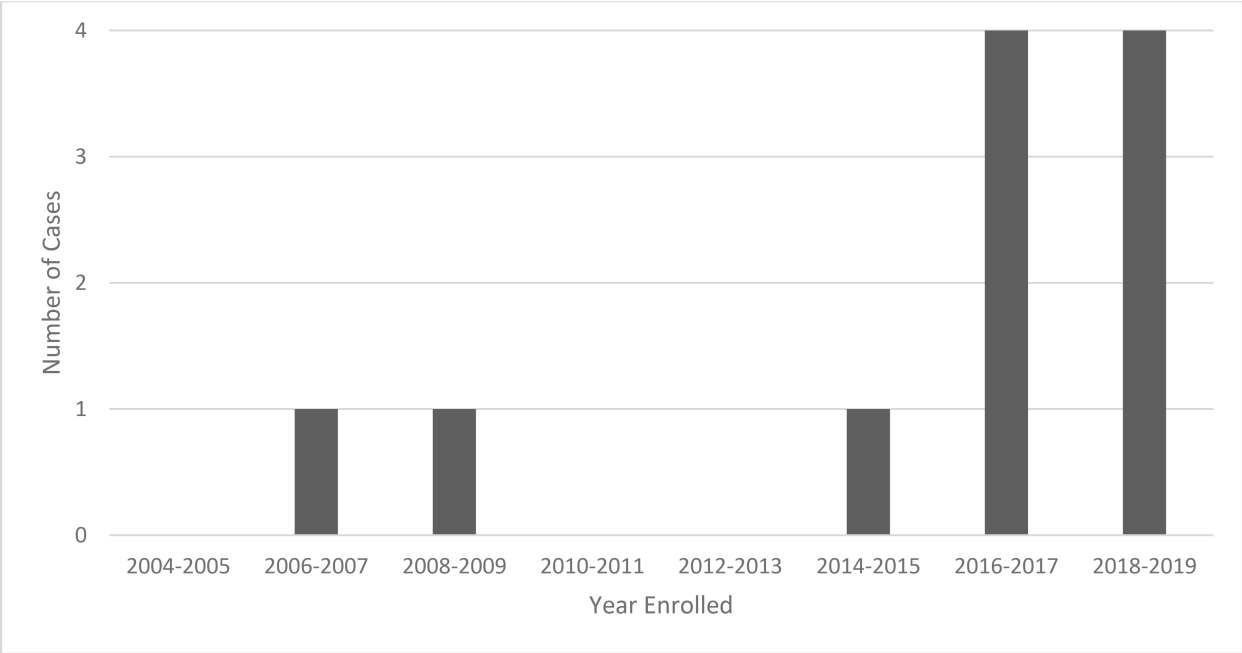

Figure 1-
Temporal trend of Kratom liver injury enrolled in the Drug Induced Liver Injury Network 2004–2019.

Table 1-

Clinical features of 11 patients with acute liver injury due to Kratom.

	Total (N=11)	
Median Age/years (range)	40 (25–70)	
Male	9	
Caucasian	9	
Median BMI kg/m^2 (range)	24.8 (20.6–28.3)	
Median Duration of use/days (range)	14 (5 – 23)	
Median Latency to symptoms/days (range)	14 (5 – 28)	
Alcohol use	7	
	Onset	**Peak**
Median ALT, U/L (range)	362 (52–1028)	406 (62–1028)
Median AlkP, U/L (range)	255 (119–360)	292 (195–836)
Median Total bilirubin, mg/dL (range)	8.9 (0.9–38.2)	11.7 (4.5–41.1)
Median INR (range)	0.9 (0.9–3.2)	1.1 (1–3.2)
RUCAM (range)	7 (2–9)	
R value at onset **Cholestatic** **Mixed** **Hepatocellular**	 2 6 3	
Median R value at onset (range)	3.2 (0.7 – 13.4)	
Median Time to recovery/days (range)	90 (34–365)	
DILIN severity score		
- 1 (mild)	none	
- 2 (moderate)	2 of 11	
- 3 (jaundice, hospitalized)	6 of 11	
- 4 (features of hepatic failure)	3 of 11	
- 5 (death or liver transplant)	none	