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Khat

Updated: April 26, 2018.

OVERVIEW

Introduction

Khat is a stimulant derived from the fresh leaves of the evergreen shrub Catha edulis, which is native to parts of East Africa and the Arabian Peninsula. Chewing khat leaves is a well established social habit in areas where the shrub is endemic and causes a mild euphoria. Khat chewing has been implicated in causing rare but serious, clinically apparent acute and chronic liver injury.

Background

Khat (pronounced "cot") is a product of the leaves of the evergreen shrub Catha edulis that is native to Ethiopia, Kenya, North Yemen and Madagascar. Chewing the leaves releases a stimulant that is absorbed through the oral mucosa and results in mild stimulation, heightened sense of awareness and euphoria. Khat chewing is a common practice and social habit, particularly among men in areas of East Africa and the Arabian Peninsula where the shrub is endemic. Recently, immigrants from those countries have introduced the practice to other areas of the world, including Europe and Australia. The active ingredient of khat is believed to be phenylalkylamine alkaloids (cathinone, cathine and norpseudoephedrine), which have sympathomimetic effects that resemble those of the amphetamines. Khat has no current medicinal use and is considered a drug of abuse with potentially serious psychological and neurological adverse effects. Khat is banned in the United States, but is legal and available in Africa, the Middle East, and some countries in Europe including the UK. Common side effects of chewing khat include excitation, confusion, decreased appetite, hyperactivity, hypertonia and hyperthermia. Chronic use has been linked to disruption of personal and family relations, depression, psychiatric problems, hypertension, myocardial infarction and stroke.

Hepatotoxicity

There is little information of whether acute or chronic khat use is associated with serum enzyme elevations or alterations in liver function. However, in recent years several individual case reports and small case series of serious acute and chronic liver injury attributed to khat have been published, largely from the UK and Europe and in immigrants from areas of the world where khat use is frequent. The onset of injury usually occurs after years of khat use and can present acutely with nausea, fatigue, pruritus and jaundice or chronically, with signs and complications of portal hypertension. The pattern of liver enzyme elevations is typically hepatocellular and, in acute cases, the aminotransferase levels can be markedly elevated. Autoantibodies occur in a proportion of cases and the disease often resembles autoimmune hepatitis with chronic inflammation and fibrosis. However, responses to corticosteroid therapy is usually only partial, at least if khat use continued. Immunoallergic features (rash, fever, eosinophilia) are not common. Some patients suffer from multiple bouts of acute injury which leads

to fibrosis and cirrhosis, portal hypertension and hepatic failure. Resolution occurs if khat chewing is stopped, but relapses are common and some patients deny relapse in khat use. While most cases have been described from Europe, chronic liver disease and cirrhosis of unknown cause are frequent in areas of the world where khat is commonly used.

Likelihood score: B (highly likely cause of clinically apparent liver injury).

Mechanism of Liver Injury

Khat leaves have multiple components, some of which may be hepatotoxic. In animals, liver injury and fibrosis have been reproduced by chronic khat exposure. Interestingly, liver injury specifically related to khat has not been reported from areas of the world where it is commonlly used, despite some studies specially focusing on the frequency of liver injury among chronic khat users. In these countries where Catha edulis is endemic and common, only freshly cut khat leaves are used and they are typically sold the day that they are harvested. Thus, the liver injury associated with khat use that has been reported from Europe and Australia may be related to the storage and shipping of the leaves, either from a contaminant or a breakdown product during storage. There is a superficial resemblance of the liver injury from khat to that of amphetamines, particularly methylenedioxymetamphetamine (MDMA, ecstasy).

Outcome and Management

The liver injury attributed to khat use can be severe and progressive, but resolution has been reported in patients who have stopped use of khat. Because khat use can result in psychological and physical dependence, stopping its regular use may be difficult. Corticosteroids are often used in patients who present with autoimmune features, but they appear to have little effect and should not be considered routine therapy. Liver transplantation has been successful in some patients, with end stage liver disease attributed to khat chewing.

Drug Class: Agents of Abuse; Herbals and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE STREET NAMES

Khat – Abyssinian Tea, Chat, Gat, Kat, Miraa, Oat, Qat, Somali Tea

DRUG CLASS

Agents of Abuse; Herbals and Dietary Supplements

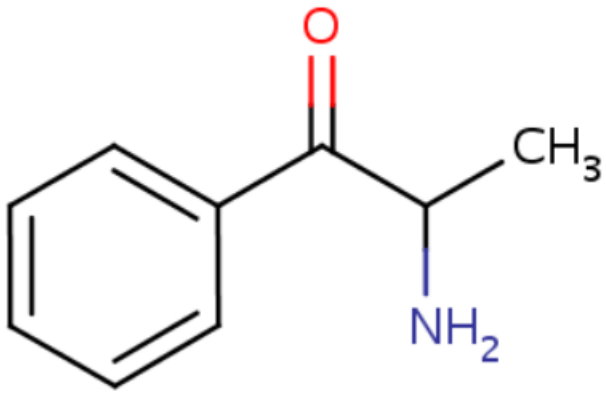
SUMMARY INFORMATION

DrugFacts at National Institute on Drug Abuse

Fact Sheet at Drug Enforcement Administration

Information at Drug & Chemical Evaluation Section, Drug Enforcement Administration

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Cathinone	5265-18-9	C9-H11-N-O	

ANNOTATED BIBLIOGRAPHY

References updated: 26 April 2018

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; discussion of hepatotoxicity of herbals and dietary supplements does not include mention of Khat).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS]; does not mention or discuss Khat).

Khat. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp 497-8.

(Compilation of short monographs on herbal medications and dietary supplements including khat).

Khakoo SI, Coles CJ, Armstrong JS, Barry RE. Hepatotoxicity and accelerated fibrosis following 3,4-methylenedioxymetamphetamine ("ecstasy") usage. J Clin Gastroenterol 1995; 20: 244-7. PubMed PMID: 7797836.

(22 year old woman developed jaundice 3 months after starting weekly MDMA abuse [bilirubin 3.1 mg/dL, AST 2314 U/L, Alk P 145 U/L, protime 16.6 seconds], and, with continued intermittent ecstasy use and 6 months later developed ascites and worsening jaundice [bilirubin 23.9 mg/dL, AST 2214 U/L, Alk P 253 U/L protime 24.1 seconds], biopsy showed fibrosis; partial response to prednisone).

Al-Motarreb A, Baker K, Broadley KJ. Khat: pharmacological and medical aspects and its social use in Yemen. Phytother Res 2002; 16: 403-13. PubMed PMID: 12203257.

(Review of the custom of khat use in Yemen and the Middle East, the chemical alkaloids present in khat leaves, the typical symptoms and side effects of its use, the adverse side effects and social role of khat chewing in society, as well as its adverse effects on personal and family life).

Chaudier B, Oliver M, Coton T, Civatte M, Guisset M, Carré, Debonne JM, Delpy R. [Chronic hepatitis with an acute presentation due to Ecstasy]. Gastroenterol Clin Biol 2002; 26: 103-4. French. PubMed PMID: 11938056.

(18 year old female developed jaundice 3 weeks after taking 2 tablets of ecstasy [bilirubin 15.6 mg/dL, ALT 44 times ULN, GGT 1.4 times ULN, protime 96%], with subsequent worsening and liver biopsy showing chronic hepatitis with bridging fibrosis; 1 year later enzymes were normal, but liver biopsy showed chronic hepatitis with mild fibrosis).

Toennes SW, Harder S, Schramm M, Niess C, Kauert GF. Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves. Br J Clin Pharmacol 2003; 56: 125-30. PubMed PMID: 12848785.

(Formal pharmacokinetic study demonstrated effective extraction of cathinone and related alkaloids [>90%] from chewing khat leaves, probable oral absorption, high rapid peak levels and half life of 1.5 hours).

Carvalho F. The toxicological potential of khat. J Ethnopharmacol 2003; 87: 1-2. PubMed PMID: 12787946.

(Editorial on toxicological profile of khat, its common side effects being withdrawal symptoms, depression, irritability, anorexia, hyperthermia and insomnia; long term use may be associated with hypertension, cardiovascular events and esophageal cancer).

D'Souza R, Sinnott P, Glynn MJ, Sabin CA, Foster GR. An unusual form of autoimmune hepatitis in young Somalian men. Liver Int 2005; 25: 325-30. PubMed PMID: 15780057.

(Comparison of clinical features of 6 Somalian men with suspected autoimmune hepatitis to 10 Caucasians with typical disease from the UK; the Somalis were more likely men [100% vs 30%], younger [mean age 37 vs 55 years], less likely to respond to corticosteroids [14% vs 80%], and less likely to have typical HLA alleles).

Al-Habori M. The potential adverse effects of habitual use of Catha edulis (khat). Expert Opin Drug Saf 2005; 4: 1145-54. PubMed PMID: 16255671.

(Review of adverse effects of chronic khat use; no discussion of hepatotoxicity).

Brostoff JM, Plymen C, Birns J. Khat--a novel cause of drug-induced hepatitis. Eur J Intern Med 2006; 17: 383. PubMed PMID: 16864024.

(35 year old East African man living in London developed jaundice and pruritus, having started using khat "recently" on a daily basis [bilirubin 10.6 mg/dL, ALT 2732 U/L, Alk P 231 U/L, ANA negative], ultimately resolving after stopping khat).

Graziani M, Milella MS, Nencini P. Khat chewing from the pharmacological point of view: an update. Subst Use Misuse 2008; 43: 762-83. PubMed PMID: 18473221.

(Review of the components, chemical structures, pharmacology and actions of khat).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% were attributed to herbals and dietary supplements, but none to khat).

Balint EE, Falkay G, Balint GA. Khat - a controversial plant. Wien Klin Wochenschr 2009; 121 (19-20): 604-14. PubMed PMID: 19921126.

(Thorough review of the history and current use of khat, its chemical constituents, pharmacology, effects and side effects; fibrosis and cirrhosis are listed as adverse effects, but not commented upon).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, of which 12 were attributed to herbals, but none to khat).

Chapman MH, Kajihara M, Borges G, O'Beirne J, Patch D, Dhillon AP, Crozier A, et al. Severe, acute liver injury and khat leaves. N Engl J Med 2010; 362: 1642-4. PubMed PMID: 20427816.

(Brief description of 6 patients who were immigrants from Africa or the Arabian Peninsula living in the UK with severe liver disease attributed to chewing khat for 6-10 years, 5 requiring liver transplant, most with multiple episodes of acute liver injury [while in the UK], resulting in liver failure [bilirubin 9.6-23.3 mg/dL, ALT 244-2314 U/L, Alk P 193-258 U/L, INR 1.3-3.7]).

Peevers CG, Moorghen M, Collins PL, Gordon FH, McCune CA. Liver disease and cirrhosis because of Khat chewing in UK Somali men: a case series. Liver Int 2010; 30: 1242-3. PubMed PMID: 20408953.

(Brief description of 7 Somalian men seen over 10 year period in a UK referral center, ages 28-41 years, with acute or chronic severe hepatocellular injury, poorly responsive to corticosteroids [bilirubin 1.8-30.4 mg/dL, ALT 636-2140 U/L, ANA positive in one]).

Stuyt RJ, Willems SM, Wagtmans MJ, van Hoek B. Chewing khat and chronic liver disease. Liver Int 2011; 31: 434-6. PubMed PMID: 21281438.

(Report of 6 cases of khat associated liver disease from the Netherlands, all patients from East Africa, some presenting with jaundice and others with portal hypertension and advanced cirrhosis, ages 17-47 years, 6 men and 1 woman [bilirubin 1.2-35.5 mg/dL, ALT 18-1192 U/L, Alk P 42-235 U/L], 4 died).

Coton T, Simon F, Oliver M, Kraemer P. Hepatotoxicity of khat chewing. Liver Int 2011; 31: 434. PubMed PMID: 20825558.

(Letter in response to Peevers [2010] mentioning that they have never seen liver injury attributable to khat, despite a large population of khat users and analysis of 204 liver biopsies from heavy users in the Djibouti Republic in the Horn of Africa).

Douglas H, Boyle M, Lintzeris N. The health impacts of khat: a qualitative study among Somali-Australians. Med J Aust 2011; 195: 666-9. PubMed PMID: 22171861.

(Interviews with members of eastern African communities in Australia found that 55% reported khat use, but often did not reveal this to physicians and caregivers).

Roelandt P, George C, d'Heygere F, Aerts R, Monbaliu D, Laleman W, Cassiman D, et al. Acute liver failure secondary to khat (Catha edulis)-induced necrotic hepatitis requiring liver transplantation: case report. Transplant Proc 2011; 43: 3493-5. PubMed PMID: 22099826.

(26 year old Somalian man with progressive liver failure visiting Belgium from the UK who was a chronic khat user [bilirubin 2.0 rising to 34.1 mg/dL, ALT 372 U/L, Alk P 337 U/L], ultimately undergoing liver transplant).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int 2012; 32: 1543-56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, herbal drugs and supplements; does not mention khat or Catha edulis).

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement. Aliment Pharmacol Ther 2013; 37: 3-17. PubMed PMID: 23121117.

(Systematic review of literature on HDS associated liver injury discusses Chinese and Asian herbs, but does not mention khat or Catha edulis specifically).

Forbes MP, Raj AS, Martin J, Lampe G, Powell EE. Khat-associated hepatitis. Med J Aust 2013; 199: 498-9. PubMed PMID: 24099213.

(32 year old Somalian man developed jaundice and pruritus and gave a history of khat use for 7 years, recently having changed his supply [bilirubin 14.0 mg/dL, ALT 1880 U/L, Alk P 161 U/L, ANA 1:640], resolving slowly, but with 2 subsequent relapses despite denial of continued khat use).

Pateria P, de Boer B, MacQuillan G. Liver abnormalities in drug and substance abusers. Best Pract Res Clin Gastroenterol 2013; 27: 577-96. PubMed PMID: 24090944.

(Review of the frequency and causes of liver test abnormalities in substance abusers, mentions that khat use can cause severe acute and chronic liver injury).

Riyaz S, Imran M, Gleeson D, Karajeh MA. Khat (Catha Edulis) as a possible cause of autoimmune hepatitis. World J Hepatol 2014; 6: 150-4. PubMed PMID: 24672645.

(Among 6 long term users of khat who presented with acute hepatitis between 2005-2010 to a single UK referral center, all were male, ages 24 to 57 years, from Somalia or Yemen and had features of autoimmune hepatitis [5 with liver biopsy], and most responding at least partially to corticosteroid therapy).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014; 60: 1399-408. PubMed PMID: 25043597.

(Among 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, the single most commonly implicated herbal agent was green tea extract; no cases were attributed to khat).

Pantano F, Tittarelli R, Mannocchi G, Zaami S, Ricci S, Giorgetti R, Terranova D, Busardò FP, Marinelli E. Hepatotoxicity Induced by "the 3Ks": Kava, Kratom and Khat. Int J Mol Sci 2016; 17: 580. PubMed PMID: 27092496.

(Review of the evidence for hepatotoxicity of kava, kratom and khat mentions the chronic liver injury that resembles an atypical autoimmune hepatitis).

Alhaddad OM, Elsabaawy MM, Rewisha EA, Salman TA, Kohla MA, Ehsan NA, Waked IA. Khat-induced liver injuries: A report of two cases. Arab J Gastroenterol 2016; 17: 45-8. PubMed PMID: 27049456.

(Two Yemeni men, 31 and 32 years old, with long term daily khat use presented with liver injury [bilirubin 5.4 and 6.1 mg/dL, ALT 400 and 275 U/L, Alk P 273 and 245 U/L, INR 1.1 and 1.4], biopsies showing interface hepatitis and fibrosis, and both improved spontaneously with stopping khat use).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 472-501. PubMed PMID: 27402097.

(Description of an online compendium of cases of liver toxicity attributed to HDS products does not include listing or discussion of khat).

Orlien SMS, Ismael NY, Ahmed TA, Berhe N, Lauritzen T, Roald B, Goldin RD, et al. Unexplained chronic liver disease in Ethiopia: a cross-sectional study. BMC Gastroenterol 2018; 18: 27. PubMed PMID: 29439653.

(Among 150 patients who presented with chronic liver disease and cirrhosis between 2015-2016 to two hospitals in Ethiopia, the cause was identified in only 67 [45%: HBV in 55, HCV in 2], and khat use was frequent both in the known and unknown etiology groups [84% vs 74%], while alcohol use was rare [9% vs 6%]).