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Khat Intertwined Liver Damage

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Abstract

Herb-induced medical illnesses including hepatotoxicity has now become a global medical and pharmacological issue. Although perceived as safe, many consequences had been associated with chronic Khat consumption. The association between the consumption of the plant Catha edulis (Khat) and acute liver injury, chronic hepatitis and cirrhosis had evidently occupied the literature. Khat induced hepatotoxicity has been recently asserted by reports of khat-induced hepatic venous thrombosis. Still remaining in the shadow is the natural history of Khat related liver damage.

Keywords: Liver damage; Khat; Hepatotoxicity

Introduction

Khat comes from the leaves and buds of Catha edulis; an evergreen shrub, that is native to the Arabian Peninsula and the Horn of Africa. The major alkaloid content of khat; cathedulins; cathinone and cathine, are having variable psycho-stimulant and euphoric effects. They structurally related to amphetamine and noradrenaline and functionally similar to amphetamine, cocaine, and sibutramine. When khat leaves chewed, cathinone and cathine are released into saliva, reaching the blood and cause pre-synaptic ejection and reuptake inhibition of dopamine from the caudate nucleus and release of serotonin from the striatum. Such alkaloids can accomplish two-thirds of the effects of amphetamine in experimental studies [1].

On behalf of immigration, the plant consumption expands to all parts of the world including Europe, North America, and Australian countries [2]. Khat has become the most commonly used psychoactive herbal, as millions of people worldwide are believed to be khat users [3]. The leaves have a sweet-smelling and taste, chewed or brewed as the tea. In fact, it's an ancient social tonic that is sacramentally being used for centuries in countries where it originally grows. Of note, fresh leaves are the preferable as drying can decompose the alkaloid content of the plant and reducing its delightful effect [4].

Also, khat leaves are chewed by students before exams in order to feel alert and it can alleviate fatigue. Experimental studies had documented a prolonged anti-nociceptive effect in animals treated with cathinone. Most recently, the mechanisms of how pain signals are attenuated have been characterized. Concerning these data, a therapeutic potential for this plant is clear [5].

Another therapeutic potential would come from the ability of cathinone in reducing the appetite without affection of ghrelin and peptide YY; the hormones which regulate feelings of hunger and satiety [6]. Contrasting amphetamine, cathinone slowly peaks in plasma, also it has a low addictive potential and no withdrawal consequences in khat quitters [7]. In the recent years, a considerable number of studies and reports have linked khat-chewing to many toxicological effects and disease conditions; hence, the plant is signified by the World Health Organization (WHO) as a drug of abuse [8]. The purpose of this paper is to highlight the damage inflicted on the liver in khat consumers.

Khat associated acute liver injury, chronic hepatitis, and cirrhosis

The publications in concern of khat-related liver damage are constantly increasing. The first report of khat-induced hepatotoxicity was in 2005, describing an African man who presented with serology negative hepatitis that improved upon khat cessation [9]. Chapman et al. reported on more severe cases with one death in his series and liver transplantation in the remaining 5 cases [10].

The report of Peevers et al. described a wide clinical and histopathological range in his series of six Somali khat consumers' immigrants from East Africa to the Netherlands. Their presentation ranged from reversible acute injuries, severe injuries to complications of cirrhosis. The investigations did not show any specific etiology for the cases with confirmed cirrhosis. Of importance, liver biopsies in five patients were compatible with the toxic origin and chronic hepatitis [11].

Jenkins et al. described two cases of acute hepatitis in chronic khat consumers. The imaging studies and serological workup did not point to specific etiology. The histopathological study of their liver tissues revealed marked lobular hepatitis with no fibrosis in case 1, wherein case 2, fibrosis was evident. Both patients improved on khat cessation [12].

In the report of Alhaddad et al. the two Yemeni khat chewers were initially diagnosed as having drug-induced hepatitis with probable Roussel Uclaf Causality Assessment Method (RUCAM) score. Their liver biopsies showed acute hepatitis on a background of chronic liver disease. Their liver function tests rapidly improved on corticosteroid treatment that was explained by the associated serological and histological features of an autoimmune process [13]. No validated laboratory test and no specific histopathological features for diagnosing khat induced hepatitis. Surely, without disclosing that the patient is a khat consumer; a specific diagnosis would be difficult and drug toxicity takes the upper hand.

In some cases, histological evidence of a background chronic liver insult had suggested chronic khat consumption and repeated subclinical hepatitis [14]. A recent report of 8 Somali men who were sequentially diagnosed as cirrhotic, testing for common causes of cirrhosis was negative. They were khat chewers and clinico-biochemical improvement has been achieved in the 4 khat quitters [15].

Another report had described a Somali man who presented with an end-stage liver disease that later on, attributed to heavy khat chewing, and he received a transplant. The pre-transplant workup revealed no etiology for the patient's cirrhosis. Wherever, the histopathological study of the explant showed cirrhosis on a background of chronic and interface hepatitis along with thrombosis of the portal and hepatic venous radicals [16]. Apparently, repeated acute hepatitis in individuals habitually chewing khat can culminate into severe liver fibrosis and cirrhosis.

Pathogenesis of Khat related hepatic damage

The natural history of hepatic damages in attribution to this plant is still unclear. In a concentration-dependent manner, khat can induce cell death, yet, the related death signaling pathways are not fully defined. Excess production of reactive oxygen radicals (ROS) had been hypothesized as a mediator of khat-induced hepatotoxicity [17]. Following exposure to khat, the generated intracellular ROS can provoke a series of signaling cascades that promote hepatocyte apoptosis [18]. Studies on leukemic cell lines had proposed khat related-induction of mitochondrial damage and enhanced autophagy as mechanisms for khat-induced cellular toxicity [19].

Khat and autoimmune liver injury

In a proportion of cases diagnosed as Khat induced acute liver injury; a range of criteria of autoimmune hepatitis have been detected. In a three Yamani patients who presented with khat related hepatitis; the serology indicative of type I autoimmune hepatitis was positive [20]. In line with this view, data from the United Kingdom revealed probable autoimmune hepatitis in 8 patients who were diagnosed as having acute hepatitis on a background of chronic khat use [21].

Impressively, the two Yemeni men in the report “khat induced liver injuries: a report of two cases” demonstrated a range of features of an immune-mediated hepatic injury [13].

Many environmental factors as viruses, drugs, and herbs have long been supposed to be triggers for autoimmune disorders in genetically susceptible candidates [22]. Leaves of Catha might act as a trigger of autoimmune hepatitis in genetically susceptible consumers. Alternatively, Immune-mediated drug injury can present as acute and chronic hepatitis with serological and histological features consistent with an autoimmune liver disease. This implication can also be applied on khat related hepatic damage [11].

Khat thrombogenicity

In a dose-related fashion, khat chewing showed an escalating independent risk factor for myocardial infarction. Indeed, this dose-response relationship argues in support of khat thrombogenicity. The analgesic quality of khat, added to the extended Khat consumption till late is portraying the evening myocardial infarctions rather than the classic early morning attacks in non-khat chewers [23,24]. Most strikingly, heavy khat chewing is carrying a 39-fold increased risk of coronary thrombosis [25].

Likewise, cerebro vascular infarctions are reported in khat users, specifically in the afternoon, coinciding with peaked plasma concentration of cathinone and in young adults as well [26].

Back to back reporting of khat-induced vascular thrombosis has spiked a great attention to an inherent thrombophilic nature of khat. The lengthening of the bleeding time by the prophylactic aspirin dosing is significantly abolished in khat chewers [27]. Adrenaline induces aggregation of human platelets, hence, cathinone in khat; *via* an adreno-stimulation effect, can abolish the anti-platelet properties of aspirin [28]. In addition, the liver tissues from khat fed rabbits showed focal areas of necrosis in hand with dilatation and congestion of the central veins and surrounding sinusoids which were filled with stagnant blood [29].

A literature review showed that case 2 in Alhaddad et al. report is the first report of adult Budd Chiari Syndrome where hepatic veins' thrombosis was proved to be a sequel of chronic khat chewing [13]. Budd-Chiari syndrome was recently reported in a 10-month-old boy after consuming cathinone containing herbal drink for 3 months [30].

In summary, Consumption of Catha edulis leaves produces a pleasurable euphoric effect and reduces fatigue and appetite. Such effects are simulated by the alkaloid content of the plant; mainly cathinone. The literature had been engaged by reports and studies which declared khat related cardio, neuro, gastro, and hepato-toxicities. Concerning khat related liver damage; the first to be described is non-viral hepatitis with variable severity, then cases of chronic hepatitis, advanced fibrosis and cirrhosis were described.

The mechanism that resides behind khat related hepatotoxicity is a hot area of research. Some cases of khat-induced liver injury showed features of autoimmune hepatitis; hence, an immune-mediated drug injury is a suggested mechanism of injury.

Budd-Chiari syndrome was recently described akin to khat consumption; however, earlier reports of cardiac and cerebral vascular thrombosis had occupied the literature and documented thrombogenicity of Khat. Currently, this seemingly benign custom is facing global concerns and strict regulations in many countries.

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