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Ecstasy: a common cause of severe acute hepatotoxicity

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Background/Aims: **Ecstasy is a synthetic amphetamine recently identified as a possible cause of acute liver injury. This drug is consumed by young people and has a marked effect on improving sociability. The extent of ecstasy-associated severe hepatic damage is unknown to date.**

Methods: **The clinical histories of 62 patients with acute liver failure admitted to the Intensive Care Liver Unit between January 1994 and December 1996 were reviewed to assess the frequency, the epidemiological, clinical and histological characteristics and the outcome of ecstasy-induced severe hepatitis.**

Results: **Over this period of time, five patients (8%) were admitted because of ecstasy-induced acute liver failure, representing 31% of the cases with drug hepatotoxicity. Ecstasy was the second most common cause of liver injury in patients under the age of 25 years, being 20% in this subset of patients and 36% after ruling out the cases of viral etiology. All the patients had severe liver disease of acute onset, with jaundice, high peak of serum transaminases activity, hypoglycemia and low prothrombin activity, but no hepatic encephalopathy. Full recovery was observed in all cases from 3 to 12 months.**

Conclusions: **Ecstasy is responsible for a relatively high number of cases of acute liver failure in young people. Therefore, the use of this drug should be investigated in all patients with severe hepatitis of unclear origin. Efforts must be made to advise young people of the risks of ecstasy consumption.**

Key words: **Ecstasy; Hepatoxicity; 3,4-Methylenedioxymethamphetamine**

3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA or ecstasy) is a synthetic amphetamine widely used as a "week-end" recreational drug because it produces euphoria, increases sociability and eliminates the sense of fatigue. It was initially considered to be a drug with few toxic effects, but in the last few years various complications and even fatal cases have been increasingly reported (1,2). Cardiac arrhythmias, disseminated intravascular coagulation, rhabdomyolisis, acute renal failure and fulminant hyperthermia are some known side effects of ecstasy. Several cases of hepatic injury associated with ecstasy use, ranging from benign forms mimicking acute viral hepatitis, to severe forms such as liver failure due to massive hepatic necrosis have also been described (1–5). Despite these severe side effects, consumption of the drug is increasing among young people in developed countries (6).

The aim of the present study was to investigate the epidemiological, clinical and histological characteristics and the outcome of ecstasy-induced severe hepatitis and to assess the relative frequency of this form of liver toxicity among patients with acute liver failure.

Patients and Methods

We reviewed the clinical histories of the 62 patients admitted to an Intensive Care Liver Unit from January 1994 to December 1996 because of acute liver failure, the diagnosis of which was based on the criteria proposed by Bernuau & Benhamou (7). Thirty-seven patients presented fulminant hepatic failure (FHF) or subfulminant hepatic failure (SFHF) according to the above-mentioned criteria (7). The remaining 25 patients did not develop hepatic encephalopathy at any time during admission, but had severe hypoglycemia and prolonged prothrombin time. During this 3-year

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ABLE 1

iology of acute liver failure in relation to age

	<25 Years (26 patients)	>25 Years (36 patients)
iral hepatitis (A, B, C or D)	12	18
oxic hepatitis	2	9
ther known etiologies	2	4
ndefined	10*	5

Ecstasy-related cases were included in this category.

period the diagnosis of ecstasy-induced acute liver failure was made in five cases.

All patients were managed according to a well-established diagnostic and therapeutic protocol (8). Physical examination was performed twice daily, and standard liver and renal function tests, prothrombin activity, plasma fibrinogen concentration, red blood cell, total and differential white blood cell and platelet counts, and urine sediment analysis were performed daily, as were chest radiographs. Blood glucose levels were tested every 2–3 h. Serological markers of acute hepatitis virus infection (IgM antibody to hepatitis A virus, hepatitis B surface antigen, IgM anti-HBc, anti-hepatitis C virus, IgM anti-cytomegalovirus, and IgM anti-Epstein-Barr virus) and antibodies against the human immunodeficiency virus were tested in all patients, as were plasma and urine copper concentration, serum ceruloplasmin, anti-nuclear, anti-mitochondrial, anti-smooth muscle and anti-LKM antibodies. Portal, hepatic and caval vein patency and absence of neoplastic disease were assessed by ultrasonography. Transjugular or percutaneous liver biopsy was performed in most of the patients. Exposure to drugs and toxic agents was systematically assessed by inquiries to patients and relatives.

Results

Etiology of acute liver failure

Based on the results of clinical investigation, the etiology of the 62 patients was attributed to: viral hepatitis in 30 (hepatitis A in four, hepatitis B in 22, hepatitis C in two and hepatitis D in two); toxic hepatitis in 11 (anti-tuberculous agents in six, paracetamol overdose in one, halothane exposure in two, erythromycin in one and *Amanita phalloides* poisoning in one); miscellaneous causes in six (autoimmune hepatitis, Budd-Chiari syndrome, Wilson's disease, lymphoma infiltration, heatstroke and fatty liver of pregnancy); undetermined origin in ten (tentatively considered as non-A-non-C hepatitis) and associated with ecstasy consumption in five. Thus, ecstasy-associated cases represented 8% of the total series of patients with acute liver failure and 31% (five of 16) of those due to a toxic agent.

Twenty-six of the 62 patients were less than 25 years old and in ten the major causes of acute hepatitis were ruled out by clinical and serological criteria. Among these ten cases, five (50%) were ecstasy related (Table 1). A slight increase in the relative frequency of ecstasy-associated hepatitis was observed during the 3-year study period, one of the 24 patients admitted in 1994, two of the 23 admitted in 1995 and two of the 15 admitted in 1996.

Clinically, they presented unspecific symptoms mimicking viral hepatitis. Following a prodromic period of a few days, jaundice and increased serum aminotransferase levels were noted. Abdominal pain was a common initial symptom, as has often been observed in "toxic" hepatitis. Three of the patients took the drug again to eliminate the sense of fatigue when they felt sick. None had eosinophilia in peripheral blood. Hepatitis was severe and associated with hypoglycemia, and the prothrombin ratio was below 50%, but none of

TABLE 2

Characteristics of the patients with acute liver injury related to ecstasy intake

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	18	19	17	19	20
Sex (male/female)	M	M	M	M	M
Peak of ALT (U/l)	2623	5282	2870	3640	2918
Peak of AST (U/l)	1755	4800	2160	2770	2970
Serum bilirubin (mg/dl)	21	38.9	24.7	27	21.9
Prothrombin index at admission (%)	30	21	23	37	27
Ecstasy consumption					
No. of tablets	1/week	1/2 weeks	2 occasions	1/week	1–2/week
Duration in weeks	4 weeks	48 weeks	–	8 weeks	28 weeks
Latency period (days)	7	7	15	7	15
Time of resolution (months)	3	12	4	8	3
Rechallenge	no	no	no	yes	no

Fig. 1. Liver biopsy showing a confluent lytic necrosis of zones 2 and 3 of acini. The limits between necrotic and preserved hepatic parenchyma is sharp. The portal tract is expanded by a dense inflamatory infiltrate (H&E×100).

these patients developed hepatic encephalopathy or ecstasy-related extrahepatic damage (Table 2).

Liver pathology

Histologic examination of the liver biopsies of the five patients showed a fairly constant pattern consisting of alterations in normal hepatic architecture due to large confluent hepatocellular necrosis present in zones 2 and 3. The portal tracts were expanded by edema and an inflammatory infiltrate, which was rich in eosinophils in two cases (Fig. 1). Focal hepatocellular necrosis and microvesicular fatty changes in preserved hepatocytes were observed in periportal areas in three cases. Canalicular bile plugs were found in two. The diagnosis of severe hepatitis was made in the five cases, and a toxic etiology was suggested in the two with tissue eosinophilia. Similar findings have been observed in most patients submitted to liver biopsy (2,3,5,9–11).

Discussion

The five cases reported here were diagnosed with ecstasy-induced hepatitis based on the following criteria: (i) Absence of epidemiological data and serologic markers to support the diagnosis of viral hepatitis (late anti-HCV seroconversion was not observed in any case). (ii) Other hepatic diseases which could produce a sharp increase in serum aminotransferases levels in young people such as autoimmune hepatitis or Wilson disease were ruled out. (iii) Exposure to the drug before the development of symptoms. (iv) Clinical improvement when the toxic agent was discontinued. (iv) Relapse in one case when the patient was again exposed to ecstasy. (vi) Pre-existing liver disease was excluded by clinical history, liver pathology and follow-up. (vii) The clinical characteristics in our cases were similar to the cases that have been previously reported (1–5,9,10,12).

The mechanism involved in ecstasy-induced hepatic injury has not yet been clearly determined. It may be related to some metabolite of the drug or to some contaminant in its preparation (11). The finding of a large number of eosinophils in the portal tracts supports the hypothesis of a hypersensivity mechanism, although fever or erythematous rash was not observed. In some cases the possibility that the hepatic lesion could be due to an ischemic mechanism, as occurs in heatstroke, has been suggested (13), since several patients presented with hyperthermia, coma and shock (1,2,13,14). This mechanism could be explained because the patients usually carry out vigorous physical exercise in enclosed places at high temperature levels. Dehydration could potentiate the effects of the drug upon the thermoregulation pathways. Interindividual variability in susceptibility to ecstasy-induced toxicity may be further explained by the existence of different phenotypes for debrisoquine 4-hydroxylase. Subjects with low debrisoquine 4-hydroxylase metabolic activity could be more vulnerable to ecstasy toxicity (15). In our cases a toxic mechanism of liver damage seems more likely because evidence of liver disease began several days after the consumption of the drug at a night party and since the pathological changes of the liver were more suggestive of a toxic etiology than an anoxic mechanism.

Some aspects of the pathogenesis of the hepatic injury associated with ecstasy remain unclear. One is the variability of the delay between last drug exposure and the onset of hepatic injury found in most reported cases, including the present series. In most cases the interval was a few days, but in others it was 2 or 3 weeks, making the measurement of the drug or its metabolites in serum or urine useless as a criterion of toxicity. The duration of use and the cumulative amount of drug consumed varied largely in patients with hepatitis associated with ecstasy. In some cases liver damage occurred after the ingestion of one or two tablets, while in others it appeared after regular use for weeks or months (Table 2). Neither was the severity of the lesions related to the length of exposure nor to the amount of drug consumed. One case of fulminant hepatitis (2) and two cases of acute hepatitis (1,3) have been described after the ingestion of just one tablet of ecstasy. Whether there is a potentiating effect of alcohol consumed in combination with the drug is still unclear.

The treatment mainly consists in conservative measures. If signs of acute liver failure develop and pro-

gress, liver transplantation should be considered. Seven reported patients have been submitted to transplantation, only three of whom have survived (1,2,5).

Patients who have had ecstasy-induced hepatitis should be warned of the danger of consuming the drug again, as they are at high risk of disease relapse, and a second episode may cause life-threatening fulminant hepatitis. There is also the risk of developing chronic hepatitis, as observed in one case (16). It is unclear whether this progression will occur if the patient does not consume ecstasy again.

According to the amount of the drug confiscated by the police, ecstasy consumption in Spain seems to be increasing dramatically in recent years (6). Since in our series ecstasy was the second cause of severe acute hepatitis in patients under 25 years of age (20% in this subset of patients, and 36% in that of unknown etiology), the number of new cases is likely to increase in the future. While in some countries paracetamol is by far the most common cause of acute liver failure, at present ecstasy accounts for the majority of severe hepatitis cases of toxic origin in our environment. Physicians should be aware of the possibility that acute hepatitis with no recognized etiology in young adults may be related to ecstasy, and should investigate and record exposure to this drug. An appropriate diagnosis allows warnings to be given regarding further exposure. When a liver biopsy is obtained, the finding of a high number of eosinophils in the portal tracts helps to determine this etiology. Young people must be warned about the risk of ecstasy consumption, and the mass media should assist in eliminating the idea that ecstasy is not a dangerous drug.

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