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Case Report

Ecstasy-Induced Recurrent Toxic Hepatitis in a Young Adult

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ABSTRACT

BACKGROUND: The drug 3,4-methylenedioxymethamphetamine (MDMA), otherwise known as "*ecstasy*," is a synthetic amphetamine that produces euphoria, increases sociability and energy, and is often used as a "weekend" recreational drug by young adults.

CASE SUMMARY: A 23-year-old male (height, 184 cm; weight, 68 kg) presented to the emergency department of Marmara University Hospital, Istanbul, Turkey, with jaundice and nausea lasting for 6 days. The patient reported that he had been a chronic user of MDMA for 2 years. He also reported that 1 week before presenting, he had ingested twice (2 tablets) the usual amount (1 tablet) of the drug at the same time. Blood tests were performed and hematologic findings were as follows: aspartate aminotransferase (AST), 1423 U/L (reference range, 10–37 U/L); alanine aminotransferase (ALT), 2748 U/L (10–40 U/L); alkaline phosphatase, 271 U/L (0–270 U/L); γ-glutamyl transpeptidase, 124 U/L (7–49 U/L); total bilirubin, 13.23 mg/dL (0.2–1 mg/dL); direct bilirubin, 8.75 mg/dL (0–0.3 mg/dL); amylase, 80 U/L (0–220 U/L); prothrombin time, 21.2 sec; activated partial thromboplastin time, 37.3 sec; and international normalized ratio, 1.66. Liver enzymes and bilirubin levels were found to be extremely high (AST = 40× normal, ALT = 70× normal, and bilirubin = 13× normal). Viral, autoimmune, and metabolic causes were excluded. Serologic tests for hepatitis A, B, and C viruses, mononucleosis, cytomegalovirus, and HIV infection were all negative. A diagnosis of ecstasy-induced toxic hepatitis was made. The patient's medical history further revealed that the current incident was actually his second occurrence of jaundice and acute hepatitis associated with the ingestion of higher amounts (twice the usual amount of MDMA he ingested at the same time). Supportive therapy (IV saline and vital sign monitoring) was initiated and liver enzymes, bilirubin levels, and prothrombin times were monitored daily. All had returned to normal values in 2 weeks.

CONCLUSIONS: MDMA, or the recreational drug ecstasy, might be responsible for acute hepatitis and/or acute liver failure, particularly in young people. Physicians might need to be alert to the possibility of ecstasy-induced liver damage occurring in

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younger patients, although the presence of other hepatotoxins and alternative diagnoses requires exclusion. The use of this drug should be investigated in young patients with severe hepatitis of unknown origin. (*Curr Ther Res Clin Exp.* 2008;69:260–265)
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KEY WORDS: 3,4-methylenedioxymethamphetamine, MDMA, ecstasy, recurrent acute hepatitis.

INTRODUCTION

The drug 3,4-methylenedioxymethamphetamine (MDMA), otherwise known as *ecstasy*, is a synthetic compound with structural and pharmacologic similarities to both amphetamines and mescaline.[1] Because it elicits feelings of euphoria, wakefulness, intimacy, sexual arousal, and disinhibition, MDMA has become a common drug of abuse, particularly among young adult party-goers.[2] For the purposes of this article, the terms "MDMA" and "ecstasy" will be used interchangeably.

MDMA is a sympathomimetic drug that causes release of endogenous catecholamines (particularly norepinephrine and dopamine) and blocks their reuptake into presynaptic vesicles.[3] The concentrations of MDMA contained in illicitly produced pills vary widely.[3] The typical dosage range for recreational use varies from 50 to 200 mg, but the actual amount per tablet in different batches of tablets might vary 70-fold or more: from almost 0 to well over 100 mg.[1,3,4] An examination of tablets sold as ecstasy in Europe between 1995 and 1997 revealed that of 69 tablets with an identifying logo, 30 contained MDMA, with doses ranging from 2 to 149 mg, and another 8 contained a mixture of substances including amphetamines, ephedrine, caffeine, and aspirin. Overall, ~10% of drugs sold as ecstasy contain no active ingredient.[5]

MDMA is typically ingested orally as a tablet and is readily absorbed in the gastrointestinal tract. Peak effects occur within 2 hours of ingestion and typically last 4 to 6 hours. Up to 75% of MDMA is excreted in the urine unchanged, while the remainder is primarily metabolized in the liver by the cytochrome P450 P2D6 (CYP2D6).[6–8] Major toxicity and death could occur after ingestion of a single tablet; ingestion of larger quantities carries greater risk for toxicity.[9] Erroneously believed to be a "safer" drug of abuse compared with amphetamine, MDMA actually shares the toxicity of amphetamine and possesses unique toxicities, both acute and chronic.[9] MDMA has also been associated with fulminant hepatic failure and should be considered in the differential diagnosis of hepatic failure in young people.[9]

We present a young patient, a chronic ecstasy user, who ingested twice his amount of ecstasy (ie, MDMA; 2 tablets at the same time) and developed jaundice and ecstasy-induced toxic hepatitis.

CASE SUMMARY

A 23-year-old male (height, 184 cm; weight, 68 kg) presented to the emergency department of Marmara University Hospital, Istanbul, Turkey, with jaundice, dark urine, and nausea lasting for 6 days. On arrival, the patient was found to be dehydrated, pale, and weak. During assessment questioning, the patient reported that he

had been a chronic ecstasy user for 2 years and usually ingested anywhere from 2 to 3 tablets of ecstasy each month while at parties, totaling 1 tablet per party night. The patient also reported that 1 week before presenting, he had ingested twice his normal amount of ecstasy tablets at the same time along with alcohol. His vital signs were as follows: blood pressure, 110/70 mm Hg; heart rate, 64 bpm; respiratory rate, 14 per minute; and body temperature, 36°C. Physical examination revealed no pathologic finding except dry and yellow skin. Blood tests were performed and results were as follows: total bilirubin, 13.23 mg/dL (reference range, 0.2–1 mg/dL); direct bilirubin, 8.75 (0–0.3 mg/dL); prothrombin time, 21.2 sec; activated partial thromboplastin time, 37.3 sec; aspartate aminotransferase, 1423 (10–37 U/L); alanine aminotransferase, 2748 (10–40 U/L); γ-glutamyl transpeptidase, 124 (7–49 U/L); alkaline phosphatase, 271 (0–270 U/L); amylase, 80 (0–220 U/L); and international normalized ratio, 1.66. Viral, autoimmune, and metabolic causes were excluded. Serologic tests for hepatitis A, B, and C virus, mononucleosis, cytomegalovirus (CMV), and HIV infection were all negative. Ceruloplasmin (0.248 [range, 0.2–0.6 g/L]), iron (150 [59–158 μg/dL]), and ferritin (227 [30–400 ng/mL]) levels were normal, and antinuclear antibodies, antimitochondrial antibody, antismooth muscle antibody, and liver-kidney microsomal antibody were also negative. Abdominal ultrasound was unremarkable. A diagnosis of ecstasy-induced toxic hepatitis was made and the patient was admitted to the emergency department. The patient did not give consent for liver biopsy.

On further questioning, the patient reported that he had previously experienced jaundice and acute hepatitis adverse events after ingestion of a higher amount than his usual ecstasy tablet dosage (ie, 2 tablets vs 1 tablet). The previous occurrence was 8 months prior to the current incident, with the same clinical status and the development of jaundice. The patient was admitted to Taksim State Hospital (Istanbul, Turkey) for 2 weeks and discharged without sequelae. Unfortunately, we could not obtain the records or laboratory results for this prior incident.

The patient's liver enzymes, bilirubin levels, and prothrombin times were monitored daily and supportive therapy (IV fluid infusion and vital sign monitoring) was initiated during the confinement period (6 days) for this current incident. The patient was followed for 1 month. Liver enzymes and bilirubin levels returned to normal values within 2 weeks (**Figure**).

DISCUSSION

Acute liver dysfunction confirmed by liver function test abnormalities might occur with infection caused by hepatitis viruses and other hepatotropic viruses (eg, CMV, herpes simplex, Coxsackie, Epstein-Barr). Other causes include a variety of toxins (eg, acetaminophen, ethanol, mushrooms, metals, various other medications), and autoimmune and metabolic hepatobiliary diseases.[10] After eliminating these specific causes, idiosyncratic drug reactions remain as other possible causes. Hepatic injury associated with MDMA (ie, ecstasy) use is one of these miscellaneous less common causes.

Several cases of hepatic injury associated with ecstasy use, with signs and symptoms ranging from benign forms that mimic acute viral hepatitis, to severe forms such as

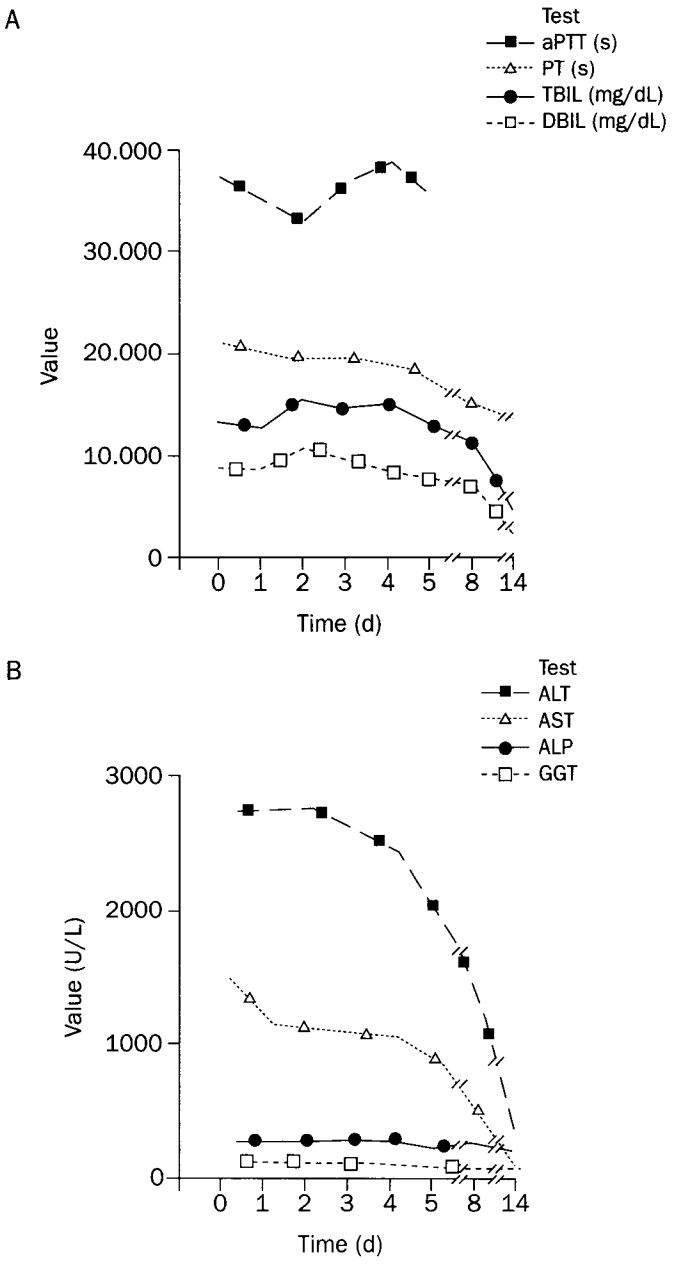

Figure. The timeline of change after ecstasy ingestion in (A) activated partial thromboplastin time (aPTT), prothrombin time (PT), total bilirubin (TBIL), direct bilirubin, and (B) related liver function tests that included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (GGT).

liver failure due to massive hepatic necrosis, have been described.[11] Our patient was diagnosed with ecstasy-induced toxic hepatitis based on having met the following criteria: no positive serologic markers to support the diagnosis of viral hepatitis; other hepatic diseases that could produce a sharp increase in serum aminotransferase levels in young people such as autoimmune hepatitis or Wilson's disease were ruled out; there was exposure to the drug before development of symptoms; there was clinical improvement when the toxic agent was discontinued; the patient relapsed when he was re-exposed to the drug based on the patient's own report; and pre-existing liver disease was excluded by clinical history and follow-up. Based on a score of 11 on the Naranjo adverse drug reaction probability scale,[12] ecstasy was the "definite" cause of toxic hepatitis in this patient.

The mechanism of ecstasy-induced toxic hepatitis has not been determined. It is believed to possibly be related to some metabolite of the drug or to some contaminant in its preparation.[13] MDMA and related drugs are largely metabolized in the liver by CYP2D6. The immediate product of this reaction is then processed further by other enzymes into a variety of secondary products, some of which are highly reactive with glutathione. A marked decrease in the level of free glutathione is related to a series of biochemical changes (eg, massive influx of calcium, oxidative change in the cell-membrane lipids) that result in cell death.[3,8] Spontaneous recovery usually occurs over a period of a few weeks to many months, but in chronic users of MDMA there could be repeated attacks of hepatitis.[3] It has been suggested that in any case of repeated acute hepatitis in a young person, the use of MDMA should be suspected as a possible cause. Andreu et al[11] found that in their hospital, ecstasy was the second most common cause of liver injury in patients under the age of 25 years. In their findings, 26 of the 62 patients studied were aged <25 years, and in 10 of these patients, the most common mechanisms associated with acute hepatitis were ruled out by clinical and serologic criteria. Further, among these 10 cases, 50% (5/10) were ecstasy related.[11] Also, genetic enzyme deficiency and immune-mediated mechanisms have been hypothesized.[9] Postmortem studies by Milroy et al[13] found that MDMA- and 3,4-methylenedioxy-*N*-ethyl-amphetamine-related fatalities were associated with hepatic, myocardial, and brain tissue damage. It has been suggested that MDMA-associated rhabdomyolysis and other organ damage occur as a consequence of hyperthermia, although Ellis et al[14] reported 8 cases of MDMA-associated liver damage, 4 in which the patients had not been hyperthermic. We do not have any evidence that our patient was hyperthermic, but the dose dependent similar clinical findings suggest that enzyme (CYP2D6) deficiency mechanism was more likely to be the cause of recurrent jaundice and recurrent toxic hepatitis.

Our patient had ingested a double dose of ecstasy with alcohol; a case in which the potentiating effect of alcohol is unknown. The exact amount of ecstasy and the contaminants are unknown as well. Further, it is not known whether toxicity is dose related.[15] One case of fulminant hepatitis and 2 cases of acute hepatitis after ingestion of just 1 tablet of ecstasy have been reported in the literature.[11] Shearman et al[16] reported a patient who developed recurrent acute hepatitis associated with repeated ecstasy use; but their patient was not a chronic ecstasy user and the condition was interpreted as an idiosyncratic response to either ecstasy or a contaminant in the preparation.

CONCLUSIONS

We report a case of recurrent toxic hepatitis in a young adult after ecstasy ingestion. Ecstasy might be responsible for cases of acute hepatitis and acute liver failure in young people. Health care providers need to be alert to the possibility of ecstasy-induced liver damage occurring in younger patients, although the presence of other hepatotoxins and alternative diagnoses require exclusion. Therefore, the use of this drug should be investigated in all patients with severe hepatitis of unclear origin.

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