Ecstasy induced acute hepatic failure. Case reports

Yahya Atayan[1], Yasir Furkan Çağın, Mehmet Ali Erdoğan, Muhsin Murat Muhip Harputluoglu[1], Yilmaz Bilgic

(1) Inönü Üniversity Gastroenterology Department, Malatya, Turkey.

Abstract

3,4-methylenedioxymethamphetamine (MDMA), an amphetamine derivative known as ecstasy, has stimulating and hallucinogenic properties. It has become a substance that is widely used especially by young people. Hepatotoxicity is one of the rare side effects of this substance and can be fatal. Ecstasy-induced fulminant hepatitis has been reported in case reports. The clinical course and the prognosis of the cases may differ. In this article, two cases in whom ecstasy-induced fulminant hepatic failure had developed and who were treated with liver transplantation, and one case which recovered with treatment, have been presented. (Acta gastroenterol. belg., **2015**, 78, **53-55**).

Key words : acute hepatic failure, exctasy.

Introduction

MDMA (3,4-methylene dioxymethamphetamine, also commonly called "Molly" or "ecstasy") is a synthetic compound with structural and pharmacological similarities to both amphetamines and mescaline. First developed in 1914 as an appetite suppressant, MDMA found use as a psychotherapeutic agent during the 1970s (1,2). However, its potential for abuse was quickly recognized. Ecstasy is a commonly abused drug, particularly among young party-goers at electronic dance music venues. The typical effects include feelings of euphoria, wakefulness, intimacy, sexual arousal, and disinhibition (3). Ecstasy is typically ingested as a tablet in dosages ranging from 50 mg to 200 mg, and it is readily absorbed from the gastrointestinal tract. Peak effects occur within two hours of ingestion and typically last for four to six hours (4). Up to 75 percent of MDMA is excreted in the urine unchanged, while the remainder is primarily metabolized by the hepatic enzyme CYP2D6 (5,6). Hepatotoxicity caused by Ecstasy poisoning is well recognized. Even in the absence of severe hyperthermia or disseminated intravascular coagulation, hepatitis, centrilobular necrosis, and hepatic fibrosis may result from Ecstasy abuse (7,8). Clinical findings are similar to other forms of toxin-induced hepatic injury and may include jaundice, abdominal pain, and vomiting. Elevations of bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT) may also be present. Encephalopathy may occur and the presentation can be that of fulminant hepatitis. Presented in this article are three cases with ecstasy-induced acute liver failure and they have been presented and discussed in the light of the literature knowledge.

Case series

First case : A 24-year-old male patient presented with jaundice in the eyes, nausea, fatigue and tiredness following use of a total of five ecstasy tablets at unknown doses two days apart one week ago. There was no history of use of alcohol, toxic drugs and herbal products by the patient. On the physical examination, the vital signs were stable ; there was abdominal sensitivity, the sclera was icteric, and there was no kayser fleischer ring on ophthalmological examination. In the laboratory analyses, total bilirubin : 14 mg/dl ; ALT : 1237 U/L, AST : 356 U/L, albumin : 3 g/dl, INR : 1.3 ; on the radiological examination, the hepatic parenchymal density was seen to be diffusely decreased and free abdominal fluid was observed in all abdominal quadrants. The spleen size was 13 cm, serum-ascites albumin gradient : 0.9, Ascitic fluid WBC : 0.7.10°3/ml cells, acute and chronic viral hepatitis (hepatitis A,B and C), cytomegalovirus (CMV), Ebstein barr virus (EBV), parvo virus markers and autoantibody (anti nuclear anticor (ANA), liver kidney microsomal (LKM1) and anti mitochondria autoantibodies (AMA)) all gave negative results. Ceruloplasmin : 0,74 g/L, serum iron : 44, ferritin : 182 μg/L. On the follow-up, the total bilirubin was 33 mg/dl (Graphic 1), direct bilirubin : 25 mg/dl, albumin : 1.8 g/dl, and the INR was increased to 3.3 and thrombocyte was decreased to 8000. The patient was placed on mechanical ventilator due to development of grade 3-4 hepatic encephalopathy on the 10th day of jaundice. With the end-stage liver disease score of 33, liver transplantation was performed from a cadaver donor on the 13th day of hospitalization. Diffuse hepatocyte necrosis was seen on liver microscopy (Figs. 1, 2). The post-transplantation trough level of total bilirubin was 8 mg/dl, albumin : 3.0 g/dl, and the INR was 1.6. The patient died while on treatment in the second week of treatment due to the increase in laboratory parameters and and development of sepsis.

Second case : An 18-year-old male patient presented with fatigue, tiredness and jaundice in the eyes after use

Correspondence to : Yahya Atayan, Inönü Üniversity Gastroenterology Department, 44100 Malatya, Turkey. E-mail : yahyaatayan@hotmail.com

Submission date : 08/08/2014
Acceptance date : 27/11/2014

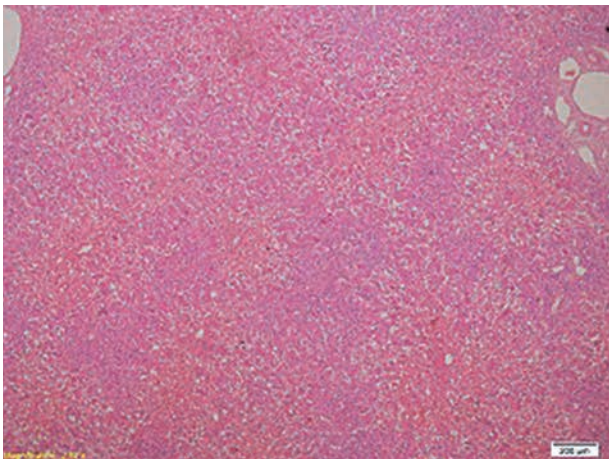


Fig. 1. — First case, liver biyopsi, in zon 2 and zon 3 widespread necrosis. H&E ×40.

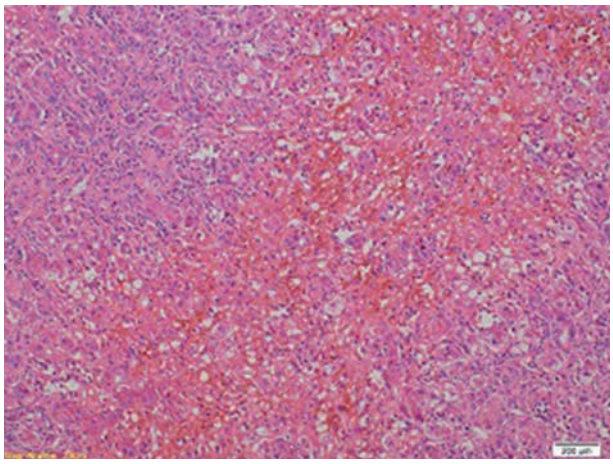


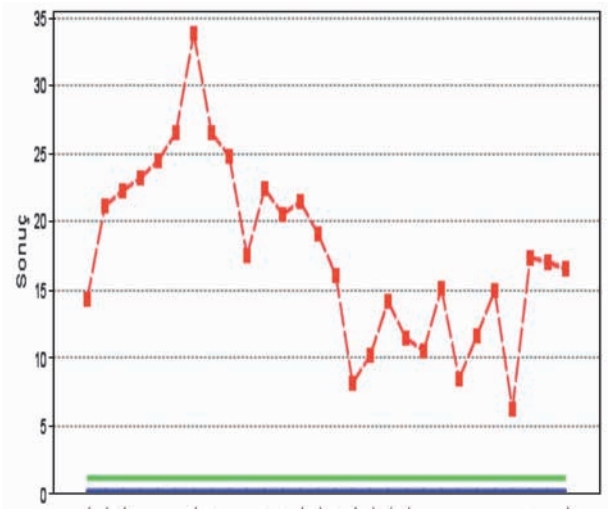
Fig. 2. — First case, liver biyopsi, mild inflammation, accompanied by perisantral and zone 2 hemorrhagic necrosis. H&E ×100.

of an ecstasy tablet once a day at an unknown dose one week ago. On physical examination, his sclera and the skin were icteric, and there was no kayser fleischer ring on the ophthalmological examination. In the laboratory parameters, creatinine was 0.7 mg/dl, albumin : 3.2 gr/dl, total bilirubin : 23 mg/dl (Graphic 2), direct bilirubin : 13 mg/dl, AST : 532 U/L, ALT : 2154 U/L, hemoglobin : 11.9 gr/dl, platelet : 177.10^3 ml, INR : 2.5, AFP : 4.4 IU/mL, ammonia : 193-266, lactate : 20, ceruloplasmin : 1.1 g/L, serum iron : 33, ferritin : 82 μg/L ; the acute and chronic viral hepatitis (hepatitis A, B and C), CMV, EBV, parvovirus markers and autoantibody (ANA, LKM1 and AMA) all revealed negative results. The patient did not have a history of alcohol, toxic drugs and herbal products use. The Liver parenchyme was found to be consistent with grade one hepatosteatosis on abdominal ultrasonography and dynamic liver tomography. As the patient developed phase 1-2 hepatic encephalopathy on the first week of the treatment, liver transplantation was performed from a living donor. Pathology of the liver parenchyme revealed diffuse hepatocyte necrosis on microscopy. The patient recovered clinically and according to the laboratory results after the transplantation, he was discharged following arrangement of his medical treatment. The patient has just been informed that his case would be published.

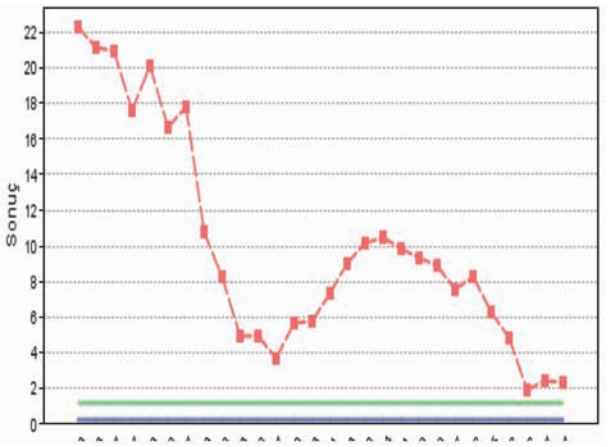
Third case : A 21 year-old male patient presented with fatigue, tiredness and nausea after use of one ecstasy tablet one week ago. On physical examination, the whole body and sclera were icteric, and there was no kaiser fleischer ring on ophthalmological examination. The laboratory results were as follows : Total bilirubin : 13 mg/dl (Graphic 3), direct bilirubin : 11 mg/dl, ALT : 1254 U/L, AST : 765 U/L albumin : 3 gr/dl, INR : 1.8, ceruloplasmin : 0,98 g/L, serum ıron : 75, ferritin : 102 μg/L ; and the acute and chronic viral hepatitis (hepatitis A,B and C), CMV, EBV, parvovirus markers and autoantibody (ANA, LKM1 and AMA) all revealed negative results. The patient did not have a history of use of alcohol, toxic drugs and herbal products. An increase in grade 1 echo was observed on the hepatic radiological examination ; On the follow-up, the total bilirubin level was 24 and INR was seen to have increased to 1.8, and as there was no development of hepatic encephalopathy, Ursodeoxycholic acid and 5% dextrose fluid were administered as supportive treatment to the patient. The patient was discharged with medical treatment after recovery had been observed on the laboratory results and his complaints had disappeared. The patient has just been informed that his case would be published.

Discussion

Ecstasy, which has stimulating and hallucinogenic properties, has become a substance widely used, especially by young people (9). Ecstasy can induce hepatological, neurological, cardiovascular, and hyperthermia syndrome complications (10). This substance has the potential to lead to acute liver failure and death (8,11, 12,13,14). Hepatic failure has been reported as part of the picture of multi-organ failure attributable to hyperpyrexia. Isolated liver damage of varying severity has also been reported. In the former, liver histology generally shows a picture of centrilobular necrosis and microvascular steatosis, a picture consistent with heatstroke (15). In isolated liver failure, the histology has been reported to be characteristic of an acute cholestatic hepatitis. The presence of eosinophils and histiocytes constitutes strong evidence for a hypersensitivity reaction (8,11,14). Encephalopathy may occur and presentation can be fulminant. Andreu and colleagues reported in one study that 31% of drug-related hepatotoxicity was attributable to ecstasy, second only to that after anti-tuberculous chemotherapy. It represented 20% of all liver failure and 36% of non-viral liver failure in patients < 25 years of age (8). The concentrations of ecstasy contained in illicitly produced pills vary widely (16). Major toxicity and death may occur after ingestion of a single tablet.



Graphic 1. — First case, total bilirubin levels



Graphic 2. — Second case, total bilirubin levels

Ecstasy-induced hepatotoxicity seems to be independent from the dose and frequency of use. However, inconsistent with the literature, acute hepatic failure developed in our first case after taking six ecstasy tablets, and in our second case after taking seven tablets in total, whereas our third case took only one tablet. It is believed as a fact that the milder form of hepatotoxicity having developed in our third case may be due to his taking a lower dose. As there can be a spontaneous recovery in cases of ecstasy-induced hepatotoxicity, some cases can be fatal. Liver transplantation was performed in some cases with fulminant course (8,12,16,17). Brauer *et al*. performed liver transplantation in an ecstasy-induced fulminant hepatitis cases and discussed 10 cases in total, including 9 other similar cases in the literature (18). 4 out of 10 cases undergoing liver transplantation died due to sepsis and the other six cases recovered after transplantation. In another series of 4 cases developing ecstasy-induced hepatotoxicity, liver transplantation was performed in two of these cases ; one of them died and the other exhibited spontaneous recovery (12). On the other hand, in the two cases of ours, spontaneous recovery could not be achieved with supportive treatment and transplantations were required. Our first case died due to sepsis after transplantation, whereas the second case is being followed-up with medical treatment after transplantation, and recovery was observed in the third case without a need for transplantation. The increase in ecstasy use, especially in the young population will increase the significance of this substance in terms of public health. While the side effects of ecstasy can cause life-threatening severe complications independent of dose, it is believed that as the dose increases, the rates of mortality and morbidity may also increase. Therefore, the use of ecstasy should be considered in people presenting with toxic hepatitis and it should be thought of as an etiological agent, especially in young adults.

References

1. CHRISTOPHERSEN A.S. Amphetamine designer drugs – an overview and epidemiology. *Toxicol. Lett*., 2000, **127** : 112-113.
2. SHULGIN A.T. The background and chemistry of MDMA. *J. Psychoactive Drugs*, 1986, **18** : 291.
3. ARRIA A.M., YACOUBIAN G.S. JR., FOST E., WISH E.D. The pediatric forum : ecstasy use among club rave attendees. *Arch. Pediatr. Adolesc. Med*., 2002, **156** : 295.
4. SHANNON M. Methylenedioxymethamphetamine (MDMA, "Ecstasy"). *Pediatr. Emerg. Care*, 2000, **16** : 377.
5. COLADO M.I., WILLIAMS J.L., GREEN A.R. The hyperthermic and neurotoxic effects of 'Ecstasy' (MDMA) and 3,4 methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype. *Br. J. Pharmacol*., 1995, **115** : 1281.
6. WU D., OTTON S.V., INABA T. *et al*. Interactions of amphetamine analogs with human liver CYP2D6. *Biochem. Pharmacol*., 1997, **53** : 1605.
7. CARVALHO M., PONTES H., REMIÃO F. *et al*. Mechanisms underlying the hepatotoxic effects of ecstasy. *Curr. Pharm. Biotechnol*., 2010, **11** : 476.
8. ANDREU V., MAS A., BRUGUERA M. Ecstasy : a common cause of severe acute hepatotoxicity. *J. Hepatol*., 1998, **29** : 394-7.
9. CARVALHO M., MILHAZES N., REMIAO F. Hepatotoxicity of 3, 4-methylenedioxy-amphetamine and methyldopamine in isolated rat hepatocytes : formation of glutathione conjugates. *Arch. Toxicol*., 2004, **78** : 16-24.
10. HENRY J.A. Ecstasy and the dance of death. *BMJ*, 1992, **305** : 5-6.
11. ELLIS A.J., WENDON J.A., PORTMANN B. Acute liver damage and ecstasy ingestion. *Gut*, 1996, **38** : 454-8.
12. HENRY J.A., JEFFREYS K.J., DAWLING S. Toxicity and deaths from 3, 4- methylenedioxy-methamphetamine ('ecstasy') usage. *Lancet*, 1992, **340** : 384-7.
13. GARBINO J., HENRY J.A., MENTHA G., ROMAND J.A. Ecstasy ingestion and fulminant hepatic failure : liver transplantation to be considered as a last therapeutic option. *Vet. Hum. Toxicol*., 2001, **43** : 99-102.
14. FIDLER H., DHILLON A., GERTNER D., BURROUGHS A. Chronic ecstasy (3,4- methylenedioxymetamphetamine) abuse : a recurrent and unpredictable cause of severe acute hepatitis. *J. Hepatol*., 1996, **25** : 563-566.
15. MILROY C.M., CLARK J.C., FORREST A.R.W. Pathology of deaths associated with 'ecstasy' and 'eve' misuse. *J. Clin. Pathol*., 1996, **49** : 149-53.
16. KALANT H. The pharmacology and toxicology of 'ecstasy' (MDMA) and related drugs : a review : *CMAJ*, 2001, **165** : 917-28.
17. JONES A.L., SIMPSON K.J. Review article : Mechanisms and management of hepatotoxicity in ecstasy (MDMA) and amphetamine intoxications. *Aliment. Pharmacol. Ther*., 1999, **13** : 129-33.
18. BRAUER R.B., HEIDECKE C.D., NATHRATH W. Liver transplantation for the treatment of fulminant hepatic failure induced by the ingestion of ecstasy. *Transpl. Int*., 1997, **10** : 229-33.