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Hepatotoxicity and Accelerated Fibrosis Following 3,4-Methylenedioxymetamphetamine ("Ecstasy") Usage

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3,4-Methylenedioxymetamphetamine ("ecstasy") has previously been reported to cause an acute hepatitis that may progress to liver failure. We present the first recorded case of ecstasy-induced accelerated hepatic fibrosis.
Key Words: 3,4-Methylenedioxymetamphetamine–Liver–Fibrosis–Drug reaction–Toxicity.

3,4-Methylenedioxymetamphetamine ("ecstasy") is commonly used at "rave" parties for its stimulatory effects. It enables the user to dance persistently throughout the night. It has been noted to cause cardiac arrhythmias (1), fulminant hyperthermia, convulsions, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure. Hepatotoxic effects have only recently been noted (Table 1) (2–5). Nine of the reported cases were of acute hepatitic reactions, leading to death in one case and liver transplantation in one other. The 10th patient had cholestatic jaundice with peripheral edema and ascites, but recovered after 3 months. This patient was also a cocaine user. The drug has not previously been noted to cause hepatic fibrosis.

CASE REPORT

A 22-year-old woman had a 1-month history of deepening jaundice, pruritus, dark urine, and pale stools. Her boyfriend had had jaundice many years previously, but there was no other history of note apart from weekly use of one tablet of ecstasy at rave parties for the previous 4 months. She denied taking any other drugs, orally or intravenously, and practiced infrequent alcohol consumption. On examination she was deeply jaundiced with a liver edge palpable 3 cm below the costal margin.

There were no other stigmata of chronic liver disease, no ascites, and no clinical evidence of encephalopathy. Investigations showed a bilirubin level of 53 μ*M* (normal <15), aspartate transaminase (AST) 2,314 IU/L (normal 6–35), alkaline phosphatase (ALP) 145 IU/L (normal 21–92), albumin 35 g/L (normal 35–55), globulin 21 g/L (normal 22-36), hemoglobin 15.1 g/L, white blood cell (WBC) count 5.3 × 10^9/L, platelet count 245 × 10^9/L, and prothrombin time (PT) 16.6 s [international normalized ratio (INR) 1.5]. IgM antibody to hepatitis A virus, hepatitis B surface antigen, and second-generation RIBA testing for hepatitis C were all negative. Ultrasound of the abdomen showed an enlarged liver only. Liver biopsy showed a hepatitic picture with severe acute and chronic active hepatitis. There was coexistent intrahepatic cholestasis and bile duct proliferation. The inflammatory infiltrate was predominantly eosinophilic, consistent with a drug reaction (Fig. 1).

Stains for iron, copper, and hepatitis B were negative. There was no evidence of α1-antitrypsin deficiency. The patient's biochemistry improved, and she was discharged home with a bilirubin level of 68 μ*M*, AST 413 IU/L, ALP 134 IU/L, albumin 40 g/L, and PT 15.3 s (INR 1.4).

She defaulted from follow-up and returned 6 months later with a 3-month history of abdominal swelling and pain and a 2-week history of worsening jaundice. She admitted to taking single ecstasy tablets on six separate occasions after discharge and before the return of her symptoms. On examination she was deeply jaundiced with a liver edge palpable 4 cm below the costal margin. Three spider naevi were noted, and she had marked ascites. Investigations showed bilirubin 410 μ*M*, AST 2214 IU/L, ALP 253 IU/L, albumin 35 g/L, globulin 25 g/L, haemoglobin 10.7 g/L (mean corpuscular volume 94.9 fl), WBC count 5.0 × 10^9/L, platelet count 164 × 10^9/L, and PT 24.1 s (INR 2.1). Serological markers for hepatitis A, B, and C were again negative. Antimitochondrial, smooth muscle, and antinuclear antibodies were negative. Ultrasound demonstrated hepatosplenomegaly with a large quantity of ascites. A repeat liver biopsy showed massive ongoing hepatocellular necrosis, again with a predominance of eosinophils. Severe hepatic fibrosis also was noted, with preservation of the reticulin pattern and an absence of nodular regeneration (Fig. 2).

Over the next 2 weeks her biochemistry improved to a bilirubin level of 388 μ*M*, AST 1,524 IU/L, and ALP 230 IU/L, but the PT increased to 30.6 s (INR 2.7). She was given a reducing course of prednisolone, and her liver function improved over the ensuing month. She was discharged home, and 4 months after her second admission is currently stable with a bilirubin level of 46 μ*M*, AST 185 IU/L, ALP 149 IU/L, albumin 35 g/L, and INR 1.4. A third liver biopsy showed extensive fibrosis, but with some evidence of hepatocellular regeneration.

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TABLE 1. *Review of reported cases of hepatotoxicity related to 3,4 methylendioxymetamphetamine usage*

Sex	Age (yr)	Details of MDMA use	Clinical presentation	Investigations	Histology	Outcome	Reference
Male	19	One table 3 wk before illness	Flulike diarrhoeal illness with jaundice	AST 1,509 IU/L GGT 103 IU/L ALP 369 IU/L Bilirubin 170 m*M*	Not available	Slow recovery	Henry et al. (2)
Female	27	Taken on three occasions	Three episodes of hepatitis each after MDMA usage	Bilirubin 400 m*M*	Not available	Full recovery	Henry et al. (2)
Female	27	Taken on at least two occasions, 4 mo apart	Two episodes of hepatitis 8–15 days after each ingestion	AST 1,717 IU/L ALP 439 IU/L GGT 50 IU/L Bilirubin 471 m*M*	Acute hepatitis; mononuclear, eosinophil, neutrophil infiltrate; centrilobular hepatocyte loss	Spontaneous resolution	Shearman et al. (3)
Male	20	Regular use for 3 mo	Jaundice and encephalopathy 2 wk after last usage	AST 2,600 IU/L Bilirubin 530 m*M*	Not available	Death	Henry et al. (2)
Male	20	Weekly ingestion of one to two tablets for 3 mo	Jaundice 4 wk after last usage	AST 2,050 IU/L ALP 201 IU/L Bilirubin 131 m*M*, increasing to 330 m*M* INR 1.5	Acute hepatitis, lymphocyte, plasma cell, eosinophil infiltrate, periportal hepatocyte loss	Recovery in 1 mo	Gorard et al. (6)
Male	19	Escalating dose over 3 mo to four tablets weekly	Jaundice and pruritus	AST 659 IU/L ALP 276 IU/L Bilirubin 181 m*M*	Not available	Slow resolution	Henry et al. (2)
Male	20	Weekly use for 10 mo	Jaundice and tender hepatomegaly	Bilirubin 40 m*M*	Not available	Resolution	Henry et al. (2)
Female	18	Weekly ingestion of one to two tablets	Acute liver failure with encephalopathy	AST 1,025 IU/L ALT 1,390 IU/L Bilirubin 480 m*M*	Acute hepatitis; massive hepatocyte necrosis; eosinophil infiltrate	Resolution after 2 mo	De Man et al. (5)
Male	19	Details unknown	Fulminant hepatic failure 1 wk after last usage	Bilirubin 400 m*M*	Not available	Successful liver transplant	Henry et al. (2)
Male	29	Taken on seven occasions (also abused cocaine)	Cholestatic jaundice, ascites, peripheral oedema	None available	Not available	Recovery over 6 mo	Henry et al. (2)

GGT, gamma-glutamyl transferase; ALT, alanine transaminase.

DISCUSSION

This patient differs from previously reported cases of 3,4-methylenedioxymetamphetamine toxicity in that she initially presented with a drug-induced acute hepatitis, which progressed to hepatic fibrosis after rechallenge. This was an accelerated panacinar fibrosis, documented over a 6-month period. Accelerated fibrosis has previously been seen in fibrosing cholestatic hepatitis, a complication of graft reinfection in patients who have undergone liver transplantation for chronic hepatitis B infection, but in these cases there is periportal fibrosis with only a mild inflammatory infiltrate (6). It has not been reported previously in drug-induced hepatitis to occur so rapidly. The cholestasis and eosinophilia would strongly suggest a drug etiology in this case (7).

Hepatic fibrogenesis is thought to be mediated by

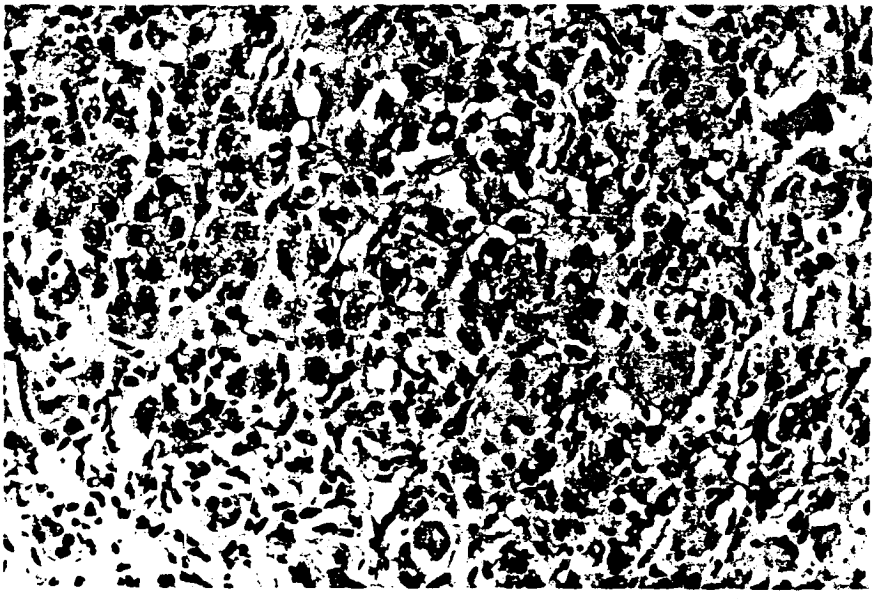

FIG. 1. First liver biopsy showing hepatocyte destruction with eosinophils in addition to mononuclear chronic inflammatory cells (hematoxylin and eosin, original magnification x 390).

lipocyte activation. Many soluble factors can mediate lipocyte proliferation and activation (8). These include transforming growth factor β1 (9), transforming growth factor α (10), epidermal growth factor (11), interleukin-1, and tumor necrosis factor α (12). Hepatocytes (13), lymphocytes, and platelets (14) are potential sources for these factors; however, 3,4-methylenedioxymetamphetamine has not yet been demonstrated to be involved in any of these pathways. The fibrosis may therefore be related to direct lipocyte activation by the drug or its vehicle, as has been shown to occur in vitro by acetaldehyde (15). It also has been suggested that parenchymal-cell necrosis itself, in the absence of inflammation, may activate lipocytes (16). The underlying mechanisms of fibrosis in this case remain unclear. Furthermore, the question of whether the toxic agent was the 3,4-methylenedioxymetamphetamine itself or its vehicle is also unanswered.

Our patient showed an idiosyncratic reaction that improved on cessation of the drug and returned after rechallenge. This case highlights the dangers of this drug, and because it is in such common usage (17) as a "party

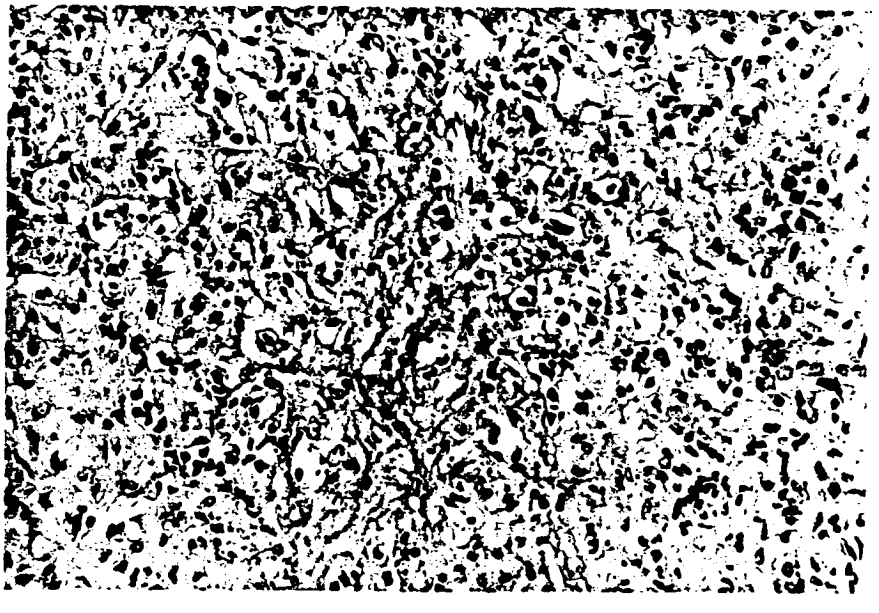

FIG. 2. Second liver biopsy showing almost total loss of liver parenchyma and replacement by fibrous tissue. A mononuclear chronic inflammatory cell infiltrate is also visible (hematoxylin and eosin, original magnification x 195).

drug", 3,4-methylenedioxymetamphetamine should be considered as a cause for unexplained liver disease in all young adults and teenagers.

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