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Review article: mechanisms and management of hepatotoxicity in ecstasy (MDMA) and amphetamine intoxications

A. L. JONES* & K. J. SIMPSON†

**Guy's and St Thomas' Hospital NHS Trust, Medical Toxicology Unit, London, and †Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh, Edinburgh, UK*

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SUMMARY

The social use of ecstasy (methylenedioxymethamphetamine, MDMA) and amphetamines is widespread in the UK and Europe, and they are popularly considered as 'safe'. However, deaths have occurred and hepatotoxicity has featured in many cases of intoxication with amphetamine or its methylenedioxy analogues such as ecstasy. Recreational use of these drugs presents an important but often concealed cause of hepatitis or acute liver failure, particularly in young people. The patterns of liver damage and multiple putative mechanisms of injury are discussed. Recognition of the aetiological agent requires a high index of suspicion. Optimum management of the resultant liver damage, including the controversial role of liver transplantation for fulminant hepatic failure, is also discussed.

INTRODUCTION

Ecstasy (methylenedioxymethamphetamine, MDMA) and amphetamine remain popular recreational drugs in the Western World. They induce euphoria, increase alertness, intensify emotions and boost self-esteem.[1, 2] Excessive dosage causes agitation, anxiety, hallucinations, coma, seizures and cardiovascular symptoms such as chest pain, palpitations and dyspnoea.[1, 2]

Hepatotoxicity has featured in several tens of cases of intoxication with amphetamine or its methylenedioxy analogues such as ecstasy (MDMA).[2–9] The evidence to date suggests that there is more than one pattern of hepatotoxicity in which different mechanisms may be responsible, and these are discussed.

CLINICAL AND HISTOLOGICAL PATTERNS OF HEPATOTOXICITY

Although cases of hepatotoxicity secondary to amphetamine ingestion have been reported in the literature, it is probable that many more are subclinical and go undetected. The clinical pattern varies from asymptomatic hepatitic liver function tests to acute hepatic failure from which some patients recover without developing encephalopathy, but others die or require orthotopic liver transplantation.[2–11] Of 342 patients admitted to the King's liver unit in London between 1993 and 1994, only two were due to ecstasy[7] and the vast majority were due to paracetamol. Of 62 patients with acute liver failure admitted to an Intensive Care Unit in Spain between 1994 and 1996, five were due to ecstasy, though none developed encephalopathy and all made a full recovery within 3–12 months of discontinuing the drug.[9] This represented the second most common cause of liver injury in patients under the age of 25 years, with viral hepatitis as the commonest cause.[9] Since the Scottish Liver Transplant unit began operating 6 years ago, 350 patients have been treated as in-patients, two patients having acute liver failure due to ecstasy (K. J. Simpson, personal communication). Some cases present with abdominal pain and jaundice secondary to cholestasis which may mimic other gastrointestinal disease such as gallstones.[2, 6, 11] One case of a dramatic accelerated panacinar fibrosis has been reported.[12] Subacute toxicity, with cumulative

Correspondence to: Dr A. L. Jones, Guy's and St Thomas' Hospital NHS Trust, Medical Toxicology Unit, Avonley Road, London SE14 5ER, UK.

hepatitic damage on recurrent exposure, has been reported after a number of ingestions of ecstasy over a number of months.[6, 11, 12] The diversity of manifestations of ecstasy or amphetamine-induced hepatotoxicity makes a recognition of the aetiological agent difficult, but it also highlights the need to consider ecstasy as a cause of unexplained liver disease in young adults and teenagers.

Hepatotoxicity may be variously manifest at a histological level as a microvesicular fatty change, small foci of cell necrosis or massive hepatic necrosis.[2, 3, 6, 13, 14]

PUTATIVE MECHANISMS OF HEPATOTOXICITY

In man, oxidation is the predominant metabolic pathway for ecstasy[15] and this reaction is catalysed by cytochrome P450 oxidase CYP2D6 in yeast,[16] and CYP2D in rats.[17] Methoxyamphetamine and hydroxyamphetamine are eliminated by cytochrome P450 oxidase CYP2D6 in man, and this would also seem to be a likely route for ecstasy.[18, 19] Unfortunately 5–9% of Caucasians lack this cytochrome as a result of an autosomal recessive inheritance of gene mutations, and they have a propensity to develop exaggerated pharmacological responses due to impaired metabolism of the parent drug.[19–21] This may be one of the reasons that accounts for the fact that whilst many 'ravers' take ecstasy, only a tiny proportion appear to develop clinical hepatotoxicity, as differences in tolerance to the drug have been reported.[22] However, immunological mechanisms may be more important in determining susceptibility to damage.

Immune-mediated mechanisms have been hypothesized to play a part in ecstasy- or amphetamine-induced liver damage as a result of the observation that rechallenge with ecstasy produced greater liver damage and this has occurred in some patients in the absence of hyperthermia.[6, 8] Liver biopsy features on one patient suggested an auto-immune hepatitis-like injury which resolved spontaneously on withdrawal of the drug.[8] The interval between drug consumption and jaundice was variable and the link was initially obscured.

If direct dose-dependent hepatotoxicity were the cause of hepatocellular damage, then surely one would have expected far more cases than the relatively few reported to date? It is likely that many cases are subclinical and therefore escape detection. Radioisotope studies have shown that amphetamine binds to parenchymal cells in the liver in preference to Kupffer cells,[23] but just because it binds, it does not mean that there is direct toxicity.

Many patients who have developed hepatocellular damage after ingesting amphetamines or ecstasy have been hyperpyrexial for several hours,[5, 6, 24] although this has not occurred in every case.[6, 14] Liver damage also occurs in heat stroke, which has as features hypotension, coagulopathy and renal impairment.[25, 26] Rat livers perfused by hyperthermic solutions show oxidative stress with superoxide formation.[27] Animals normally react to hyperthermia by the rapid transcription and translation of heat shock proteins which help the cell to survive thermal stress.[28-31] Subcutaneous administration of amphetamine to rats caused hyperthermia but no induction of heat shock protein in the liver.[32] Thus the liver may have impaired thermotolerance when amphetamine is present, whereas other organs may be unaffected. Lipid peroxidation, due to functional abnormalities of hepatic mitochondria, has been proposed as the cause of liver damage associated with cocaine use, and microvesicular fat has also been reported in some patients who died after ecstasy or amphetamine intoxication.[6] Interestingly, cocaine has an almost identical clinical effect to amphetamines when taken in excess,[33–35] and lipid peroxidation has also been reported in military recruits with fatal heat stroke.[36] Therefore, the concept that failed protection against heat induces damage by lipid peroxidation remains a significant aetiological possibility.

Incubation of hepatocytes with D-amphetamine induced a concentration dependent glutathione depletion which was prevented by pre-treatment with the P450 enzyme inhibitor metyrapone in rats.[17] However, the glutathione depletion did not lead to an alteration in cell viability or lipid redox status,[17] but liver glutathione status may perhaps affect susceptibility to amphetamines; for example, those who have an intercurrent viral infection could be more susceptible to hepatic injury.

Hepatic damage has followed the intravenous misuse of methamphetamine and amphetamine[3, 37–39] but this was probably a result of viral infection by Hepatitis B or C due to contaminated needles.[38] Necrotising angiitis has also been reported in number of cases of drug abuse and a variety of factors, including hepatitis B or C infection,[40–43] as well as methamphetamine sensitivity,[41] may be responsible. Necrotising angiitis is usually characterized by severe pancreatitis, renal failure, hypertension, pulmonary oedema and neuropathy which have not been the dominant feature in any of

the cases of hepatocellular damage from amphetamines or ecstasy to date.

There is no evidence for haemodynamic alterations to liver blood flow in amphetamine or ecstasy intoxication, but systemic hypotension might compound other consequences of poisoning, particularly hypoxia, should ecstasy or amphetamine constrict the hepatic artery, reduce portal blood flow or cause porto-systemic shunting.[44]

With illicit drugs, the possibility of a hepatotoxic contaminant can never be excluded but none has been identified.[14] There is no evidence that patients are more likely to succumb after switching their supplier of ecstasy.

RECOMMENDED MANAGEMENT FOR HEPATOTOXICITY FROM ECSTASY OR AMPHETAMINE INTOXICATION

Because of the multiple clinical and histological hepatic changes induced by ecstasy or amphetamine, it is important to exclude other hepatotoxins such as drugs (especially paracetamol), viruses (hepatitis A, B, C, Cytomegalovirus and Herpes), Wilson's disease, haemochromatosis, alpha-1 antitrypsin deficiency, portal and hepatic vein thrombosis, and auto-immune liver disease. Alcohol abuse, which may be covert, must also be excluded. The toxin should be confirmed in urine by an initial screening test such as Syva EMIT immunoassay (Boehring Diagnostics, Milton Keynes, UK), and subsequent confirmation in blood or urine by gas chromatography and mass spectrography. However, the ingestion/presentation interval and short half-life of the drug frequently lead to a negative result. If any tablets of the batch are remaining, they should also be subjected to analysis.

The degree and extent of liver injury should be monitored by serial prothrombin time estimations and liver function tests, including bilirubin, aminotransaminases and albumin. Liver biopsy should be considered if the extent of liver damage or aetiology is in doubt. This should be carried by the transjugular route where there is significant prolongation of the prothrombin time. A high number of eosinophils may be found in the portal tracts.[9] Accurate clinical assessment of renal function—that is, more than simply monitoring plasma urea and electrolytes, is also required. Meticulous supportive care is critical to good outcome.

Hyperthermia should be treated aggressively with cold fluids, but care should be taken to avoid provocation of hyponatraemia which may be due to anti-diuretic hormone release.[45, 46] The role of dantrolene is controversial.[47–51] It acts to control calcium release at the sarcoplasmic reticulum and thus reduce the 'muscular' source of heat. However, hyperthermia from amphetamines or ecstasy is also attributed to a central hyperthermic effect and there is no evidence that dantrolene has any action in the central nervous system (CNS). Rodent studies suggest there is a rationale for use of ketanserin, as a specific $5HT_2$ agent to reduce CNS-induced hyperthermia, but no clinical trials have been undertaken to date.[52]

Systemic hypotension which may reduce liver blood flow should be avoided with judicious fluid and pressor support.[44] The use of N-acetylcysteine has not been evaluated. It is unlikely to be of theoretical benefit, unless one postulates glutathione depletion as contributing to hepatotoxicity, though other potentially helpful mechanisms of action, such as free radical scavenging, may be of benefit in patients with fulminant hepatic failure.[53] Similarly, the role of steroids in cases postulated to have an immune component has not been properly evaluated, although they probably have rationale in cases where re-challenge with the drug produces significant hepatotoxicity. Once a viral aetiology has been excluded, a therapeutic trial with high dose steroids, for example prednisolone 40 mg/day, is worthy of consideration in such patients. Amphetamine- or ecstasy-induced cholestasis may resolve spontaneously, even after several months.

The role of liver transplantation in acute liver failure is very controversial and emotive. This is due to the age of the patients involved in ecstasy/amphetamine intoxication and the role of 'self-abuse' in the aetiology of liver failure, and thus the potential for continued high risk behaviour post-transplantation. Orthotopic or auxiliary liver transplantation has been performed on patients with acute liver failure due to ecstasy use, but the reported numbers are too small for the success to be evaluated and not all patients may have been referred in time. The overall survival of patients transplanted for acute liver failure is in the order of 80% at 1 year. However, survival following liver transplantation for drug-induced liver failure may be as low as 15%, even in experienced transplant centres.[54] Of five patients who fulfilled the criteria in the Ellis study,[6] one died before an organ became available, three were transplanted and died within a month of overwhelming sepsis, and only one survived. A successful transplantation has been reported in a small number of patients but the

maximum period of follow-up was not very long (maximum period 18 months).[2, 9, 11, 55] These poor survival figures have to be considered in the light of a contracting donor pool and mortality of patients with chronic liver disease (with potentially much higher survival post-transplantation).

In the UK, the presence of drug-induced acute liver failure is considered a poor prognostic feature. The association with two of the following four features are considered an indicator for emergency liver transplantation: jaundice to encephalopathy developing over more than one week, age below 10 years or above 40 years, serum bilirubin > 300 μmol/L and prothrombin time greater than 50 s.[56] A prothrombin time greater than 100 s is also considered an indication for orthotopic liver transplantation.[56] It is important that patients with fulminant hepatic failure due to ecstasy or amphetamine usage are discussed and referred to a liver transplant unit at an early stage.

SUMMARY

Physicians should be alert to the possibility of ecstasy- or amphetamine-induced liver damage occurring in younger patients, although the presence of other hepatotoxins requires exclusion. Hepatotoxicity due to these drugs should be managed conventionally with meticulous supportive care, but in addition rigorous rehydration and active cooling measures should be employed. The aetiology of the hepatocellular injury is probably multifactorial but both immune-mechanisms and hyperthermic liver injury probably play a part. The benefit/risk ratio of orthotopic liver transplantation for fulminant hepatic failure remains in question but early discussion of cases with a liver transplant unit is advised. The role of steroids has not been assessed but they may be beneficial because of the autoimmune component of the hepatotoxicity in some cases.

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