Importance of early identification of methylenedioxymethamphetamine ('ecstasy') ingestion in victims of motor vehicle accidents

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The blood of motor vehicle accident victims is routinely screened upon their arrival at the emergency services mainly for alcohol, unless the suspicion of a specific compound arises. Two young men who sustained severe internal and orthopaedic injuries after a motor vehicle accident are described. The conscious patient denied their having used stupefacients, but toxicological analysis upon arrival at the operating room detected methylenedioxymethamphetamine, the metabolite methylenedioxyamphetamine and methamphetamine in their blood and urine specimens. Methylenedioxymethamphetamine concentrations in the clotted blood and in the urine ranged between 0.9–1.15 and 55–70 mg/l, respectively. Methylenedioxyamphetamine concentrations for both patients were less than 0.2 mg/l in the blood and 2.0–3.0 mg/l in the urine. Each had a blood methamphetamine concentration greater than 250 ng/ml. There was no trace of alcohol. Three days after their arrival at the hospital, acute liver insufficiency and mild rhabdomyolysis (serum glutamate-pyruvate transaminase/serum glutamic-oxaloacetic transaminase 1245/218 mU/ml, creatine phosphokinase 48 000 U/ml, respectively) were diagnosed in both patients. Appropriate treatment was administered in an intensive care area and both were discharged home several weeks later without sequelae. These findings suggest that in this era of the widespread abuse of 'ecstasy', concentrations of methylenedioxymethamphetamine, methylenedioxyamphetamine or metamphetamine should be sought routinely in motor vehicle accident victims admitted to emergency services with an altered state of consciousness so that the early monitoring of the potential development of organ pathology can be implemented. ***European Journal of Emergency Medicine*** **10:19–22 © 2003 Lippincott Williams & Wilkins.**

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Introduction

Alcohol has for many years been a major abuse substance responsible for motor vehicle accidents (MVA) among adolescents and youngsters. As a result, blood screening for alcohol has become a routine procedure in MVA victims upon their arrival at the emergency services. Ecstasy (Adam, 3,4-methylenedioxymethamphetamine; MDMA) has become increasingly popular at all-night dancing parties because of its properties as a potent stimulant and hallucinogen. The present report describes severe traumatic crush injuries of two young men after an accident involving the car driven by one of them while under the influence of ecstasy, and proposes the inclusion of MDMA among the substances routinely analysed by the emergency services. The early detection of the presence of even low blood levels of MDMA will enable the early monitoring of the hepatic and renal pathologies associated with this drug and the prompt implementation of treatment to minimize their sequelae.

Case report

A 29-year-old man suddenly steered his vehicle off the road and crashed into an electric pole. He suffered severe injuries to the head, lower limbs and chest and was unconscious (Glasgow Coma Score; GCS 5) upon arrival at the emergency services. The second patient, a 26-year-old male passenger, was found to be lethargic (GCS 11) and suffering from a lower-limb crush injury as well as mild lacerations of the skin of the skull.

Early clinical findings

The first patient arrived at the operating theatre, sedated and ventilated, with a GCS of 3. His pupils were 3 mm wide and slightly responding to light, he was tachycardic (134 beats/min), and systolic blood pressure ranged between 156 and 184 mmHg. Arterial blood gases indicated good oxygenation, normocarbia and mild metabolic acidosis (pH 7.31, base excess (BE) −6.4) with no detectable pulmonary shunt. Laboratory tests were normal except for haemoglobin of 8.2 g%. He underwent a burr hole procedure and the insertion of a subdural intracranial pressure (ICP) monitoring device as a result of left occipital subdural haematoma and signs of increased ICP on the computerized axial tomography (CAT) scan. The abdominal imaging scan detected a splenic subcapsular haemorrhage, which the surgeons

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decided to keep under observation. A right-sided chest tube was inserted because of the haemothorax that was visualized on the chest X-ray and CAT scan. His bone fractures underwent external fixation while undergoing neurosurgery. The postoperative period was complicated by stormy unrest accompanied by a dangerous increase in the ICP level (maximum 28 mmHg), fever (up to 38.5°C) and the suspicion of intracranial re-bleeding. This necessitated both re-intubation and the administration of sedatives and muscle relaxants to enable satisfactory ventilation and a new brain CAT scan. Fortunately, conservative treatment, i.e. sedation and relaxation, external and internal (intraperitoneal) body cooling, normocarbic ventilation and osmotic diuresis, and daily CAT scans, brought about an amelioration of the neurological and clinical symptoms and signs (e.g. calmness, a lowering of the ICP). Two days later, the CAT scan indicated no abnormal intracranial findings, and the patient was allowed to wake (GCS 12) with only a mild motor deficit in his left hand.

The second patient arrived at the operating room in a sleepy but arousable state. He had a GCS of 14, the arterial blood gases were normal and he was breathing air-enriched 40% oxygen via a face-mask (BE −2.1). The pupils were of normal width and responded to light; systolic blood pressure was slightly but constantly above the upper normal limit (150–175 mmHg), and the heart rate was approximately 110 beats/min. Laboratory tests were normal except for haemoglobin of 10.1 g%. He stated that he could remember there having been an accident but denied being aware of the cause. He also denied any previous alcohol consumption or drug usage. A CAT scan excluded brain, chest or abdominal lesions. He underwent a repair of his broken right patella and tibia and of the broken left fibula.

Before each patient entered the operating room, samples of blood and urine were taken for laboratory, toxicological and immunological tests as well as for blood typing, the usual protocol for trauma patients undergoing emergency surgery.

Toxicological analyses

MDMA and its metabolite 3,4-methylenedioxyamphetamine (MDA) toxicological analyses were conducted on blood and urine, using a combination of multiple enzymatic immunoassay (EMIT; EMIT, Wroclaw, Poland) for abused drugs, thin-layer chromatography (Toxilab; Ansys Technologies Inc., Lake Forest, CA, USA), and enzymatic methodology for the quantitative measurement of ethylalcohol (Vitros ALC Slides; Johnson and Johnson Clinical Diagnostics, Rochester, NY, USA; using the Kodak 250 Analyzer; Kodak, NY, USA). Methamphetamine in the patients' fluids was analysed using a qualitative quick test (SureStep; Applied Biotech Inc., San Diego, CA, USA). Gas chromatography–mass spectrometry was used for the confirmation and quantification of the substances. Detection of HIV was obtained by the Abbott HIV 1/2gO EIA enzyme-linked immunosorbent assay method (Abbott Diagnostics, Weisbaden, Germany). Previous exposure to hepatitis was determined by the Microparticle Enzyme Immune Assay method (HbsAg-V2 for the presence of hepatitis B surface antigen) and by antibodies to hepatitis C (HCV-V3), both using the AXSYM system (Abbott Diagnostics). Measurements of MDMA, MDA and metamphetamine by gas chromatography–mass spectrometry were performed as described previously by Crifasi and Long [1]. The MDMA, MDA and amphetamine concentrations in the specimens submitted for analysis are shown in Table 1.

Late clinical and laboratory findings

Blood tests were repeated on day three of the patients' stay in the hospital. The results for patient no. 1 showed signs of an evolving acute hepatic insufficiency as expressed by a rise in hepatoenzymes (serum glutamate-pyruvate transaminase/serum glutamic-oxaloacetic transaminase 1245/218 mU/ml) and total bilirubin (1.3 mg/dl); the international normalized ratio level was above normal (2.3). Severe intermittent hypoglycaemia (down to 42 g%) was also detected. There was also a sign of a developing rhabdomyolysis in the creatine phosphokinase (CPK) value was as high as 48 000 U/ml on that day. The patient was re-admitted to an intensive care area. All these values began to decrease slowly during the next 5 days, after the implementation of an aggressive renal protective therapy (large infusion load, forced diuresis by mannitol and furosemide, alkalinization of the urine to a pH > 7.0). Four-hourly blood samples were taken for hepatoenzymes, glucose and potassium levels; seizures did not develop but low-grade fever (37.6–37.9°C) recurred. The patient was also given two units of fresh frozen plasma. The results of these same tests for patient no. 2 showed a mild increase in hepatoenzymes

Table 1 **Toxicological data**

Specimen	MDMA (mg/l)		MDA (mg/l)		Methamphetamine (ng/m)		Alcohol (g%)	
Patient	1	2	1	2	1	2	1	2
Blood (clotted)	1.15	0.9	<0.2	<0.2	>250	>250	0	0
Urine	60	55	<3.0	>2.0	>500	>500	0	0

MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-Methylenedioxyamphetamine.

and CPK, which, however, decreased within a few days without intervention. His body temperature increased to a maximum of 38°C without accompanying seizures or signs of infection. This patient was then admitted to an intensive care area, was invasively monitored, and was cooled actively (cover sheets soaked with cold saline mixed with alcohol 70%). The hepatitis and HIV tests were negative for both patients.

The two patients now admitted having taken, for the first time, two ecstasy tablets (i.e. 200 mg) during a party on the eve of the accident.

Discussion

An exhaustive multi-language MEDLINE search failed to reveal any earlier publication that demonstrated an association between MDMA ingestion and severe, non-fatal MVA having being determined upon admission to emergency services. The rate of MVA among people aged less than 30 years is much higher than for older individuals [2]. This age margin also distinguishes those who are more prone to abuse drugs (e.g. ecstasy) than less [3]. Given those statistics, together with the current findings, it is proposed that any young and apparently healthy individual who presents at the emergency department in an altered state of consciousness, who suddenly collapsed during dancing and has unexplained fever, or who is an MVA victim, should be suspected of having ingested ecstasy and be worked up and treated accordingly, or at least be regarded as being intoxicated until diagnosed otherwise.

MVA in patients who have ingested ecstasy and who claim to have suddenly lost coordination or clear vision of the road are sometimes independent of blood levels of MDMA or its metabolite MDA. Indeed, the average of blood concentrations was less than 0.2 mg/l (0.18 ± 0.14 mg/l) in the report by Omitzigt *et al.* [4] on nine individuals who were involved in MVA while under the influence of MDMA. Bost [5] described a fatal accident in which the driver's levels of MDMA ranged between 0.95 and 2.0 mg/l. The effects of ecstasy can also be concealed by different signs or features: Dowling *et al.* [6] reported two fatalities, an asthmatic patient with an MDMA level of 1.1 mg/l (natural cause of death) and a patient with an acute MDMA intoxication at 1.0 mg/l with a 0.04 g/% level of ethanol (MDMA intoxication was later considered to be the cause of death). Hooft and van de Voorde [7] also reported a fatality caused by reckless behaviour, which may result from the euphorogenic activity of ecstasy; later blood analysis revealed a MDMA level of 0.63 mg/l and a blood alcohol concentration of 0.123 g%. The two currently reported patients had toxic blood and urine concentrations that are consistent with these reports, indicating that near fatality may occur during driving after the ingestion of even a small dose of ecstasy, as a result of faculty impairment by MDMA, even if very little MDA was traced in the patients' fluids. Finally, a recent study of volunteers [8] showed a 13% increase in the plasma concentration of MDMA and a longer lasting euphoria and well-being than after MDMA or alcohol alone.

The high ratio of serum glutamate-pyruvate transaminase to serum glutamic-oxaloacetic transaminase in the two reported patients is highly indicative of abnormal hepatic function. An extrahepatic pathophysiological mechanism for the observed hepatotoxicity could be the hyperthermic injury combined with liver ischaemia that could have been induced by hypoperfusion and severe sweating during the party that preceded the ill-fated drive, all leading to hepatocellular damage such as that occurring after MDMA intoxication [9]. A similar hypermetabolic state is, indeed, associated with muscle contraction and the high serum CPK activity that was also detected in the reported patients. Thrombocytopenia could also be associated with this complex event. Other possible explanations for MDMA-induced liver injury include enhanced lipid peroxidation, similar to that seen in cases of cocaine intoxication, insofar as these two drugs have similar central and enzymatic effects [10], or idiosyncratic toxic hepatitis caused by MDMA, its metabolites or a contaminant that may infiltrate into the compound during the manufacture of MDMA [11]. Indeed, MDMA was found to be the second most common cause of liver damage in patients under the age of 25 years, and the cause of drug-induced severe hepatotoxicity in up to 31% of cases [12]. In very rare severe hepatic failure, liver transplantation should be considered [13]. Moreover, metabolic differences among individuals could explain differences in drug susceptibility, because the drug is metabolized by cytochrome P_{450} [9,14]. This is another reason for an expeditious recognition of the true cause of MVAs in these patients. Finally, alkalinization of the urine would delay the effects of MDMA and its metabolites so that prolongation of the toxic manifestations could occur (e.g. fever). Nevertheless, it must be borne in mind that whereas all the above-mentioned symptoms and signs were attributable mainly to MDMA intoxication, they are also the possible consequences of multiple organ and crush injuries, such as those sustained by the two patients.

In conclusion, the half-life of MDMA ranges between 6 and 8 h [15], which would further support an acute administration in the presence of very little MDA being detected in the reported patients. This range allows enough time to identify the abused drug approximately 8 h after drug ingestion. A single sample of blood, urine and saliva [16] will provide sufficient evidence to circumvent significant and permanent organ failure. Moreover, although possibly identified in the urine

2 days after intake, the identification of the presence of ecstasy upon arrival at the emergency services would point to the necessity for short-term recovery in an intensive care area, full monitoring and preventative system-oriented management in order to limit the deleterious effects of hepatic insufficiency and CPK in the kidney in addition to those inducible by multiple organ trauma.

References

1 Crifasi J, Long C. Traffic fatality related to the use of methylenedioxymethamphetamine. *J Forens Sci* 1996; **41**:1082–1084.

2 Aharonson-Daniel L, Avitzour M, Barell V. Road traffic accidents. Circumstances, diagnoses and severity of injury – data from the Israeli National Trauma Register [in Hebrew]. Harefua 2001; 140:919–922; comments 140:938.

3 Marquet P, Delpla PA, Kerguelen S, *et al.* Prevalence of drugs of abuse in urine of drivers involved in road accidents in France: a collaborative study. *J Forens Sci* 1998; **43**:806–811.

4 Omitzigt JG, Vennaase CJ, Zweipfenning GM. *Deaths associated with amphetamine, 3,4-methylene-dioxymethamphetamine (MDMA), 3,4-methylenedioxyethamphetamine (MDEA) or 3,4 methylenedioxyamphetamine (MDA) abuse*. Tampa: Society of Forensic Toxicology; 1994.

5 Bost RO. 3,4-Methylenedioxymethamphetamine (MDMA) and other amphetamine derivatives. *J Forens Sci* 1988; **33**:576–587.

6 Dowling GP, McDonough ET, Bost RO. Eve and ecstasy: a report of five deaths associated with use of MDEA and MDMA. *JAMA* 1987; **257**: 1615–1617.

7 Hooft PJ, van de Voorde HP. Reckless behaviour related to the use of 3,4-methylenedioxymethamphetamine (ecstasy): apropos of a fatal accident during car-surfing. *Int J Legal Med* 1994; **106**:328–329.

8 Hernandez-Lopez C, Farre M, Roset PN, *et al.* 3,4-Methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics. *J Pharmacol Exp Ther* 2002; **300**:236–244.

9 Jones AL, Jarvie DR, McDermid G, Proudfoot AT. Hepatocellular damage following amphetamine intoxication. *J Toxicol Clin Toxicol* 1994; **32**:435–444.

10 Kloss MW, Rosen GM, Rauckman EJ. Cocaine-mediated hepatotoxicity. A critical review. *Biochem Pharmacol* 1984; **33**:169–173.

11 Graeme KA. New drugs of abuse. *Emerg Med Clin North Am* 2000; **18**:625–629.

12 Andreu V, Mas A, Bruguera M, *et al.* Ecstasy: a common cause of severe acute hepatotoxicity. *J Hepatol* 1998; **29**:394–397.

13 Garbino J, Henry JA, Mentha G, Romand JA. Ecstasy ingestion and fulminant hepatic failure: liver transplantation to be considered as a last therapeutic option. *Vet Hum Toxicol* 2001; **43**:99–102.

14 Delaforge M, Jaousen M, Bouille G. Inhibitory metabolite complex formation of methylenedioxymethamphetamine with rat and human cytochrome P450: particular involvement of CYP2D. *Environ Toxicol Pharmacol* 1999; **7**: 153–158.

15 Baselt RC, Cravey RH. *Disposition of toxic drugs and chemicals in man*, 4th ed. Chicago: Year Book Medical; 1995. p. 508.

16 Navarro M, Pichini S, Farre M, *et al.* Usefulness of saliva for measurement of 3,4-methylenedioxymethamphetamine and its metabolites: correlation with plasma drug concentrations and effect of salivary pH. *Clin Chem* 2001; **47**:1788–1795.