Murthy 97B

Biochemical implications of ecstasy toxicity

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Increasing numbers of young people are being admitted to accident and emergency (A&E), departments with complications following the use of the hallucinogenic drug ecstasy (3,4 methylenedioxymethamphetamine; MDMA). Recreational use of ecstasy is associated with a definite morbidity and mortality.[1,2] We report a case of ecstasy toxicity with severe multiple organ failure, who went on to make a full recovery after prolonged hospitalization. The causes and implications of various biochemical changes and the relevance of serum creatine kinase activity and its isoforms are discussed.

CASE HISTORY

A 21-year-old healthy male was admitted to the A&E department following collapse at a night club dance party with friends. The patient was reported to have taken seven tablets of ecstasy, 2 g of speed (amphetamine) and alcohol, 5 h prior to collapse. Past medical history was unremarkable. No family history of anaesthetic problems was noted.

On arrival, he was unconscious with a Glasgow coma score 3 and a core temperature of 42 °C. He was sweating profusely, had muscle rigidity and dilated pupils. Other significant findings were: pulse rate 170 beats/min, blood pressure 85/60 mm Hg and respiratory rate 42 breaths/min. Immediate therapy included oxygen through a face mask, resuscitation with 2 L of cold 0·9% saline intravenously and endotracheal intubation and ventilation prior to admission to the intensive care unit (ICU). Initial investigations revealed a haemoglobin (Hb) concentration of 15·1 g/dL with normal blood urea, electrolytes and coagulation studies, but serum creatine kinase (CK) was elevated (6111 U/L). Arterial blood gas analysis showed a combined metabolic acidosis and respiratory alkalosis. Toxicological analysis confirmed ecstasy ingestion with a MDMA plasma concentration of 0·75 mg/L and methylenedioxyamphetamine (MDA) plasma concentration of 0·025 mg/L (National Poisons Unit, UK). Blood alcohol was not measured and serum paracetamol and salicylate were not detected.

On the ICU, he was sedated with infusions of propofol and alfentanil, paralysed with an infusion of atracurium and ventilated. Resuscitation with cold intravenous fluid was continued to maintain a urine output of 200–400 mL/h and hyperpyrexia was successfully controlled with two doses of dantrolene 120 mg and sponging with ice cold water. When myoglobin was detected in the urine, an infusion of 10% mannitol was started. Alkalinization of urine with an infusion of 1·4% sodium bicarbonate was given to maintain a urine pH between 6–8. Four hours after admission, he showed a mild coagulopathy and hypocalcaemia (adjusted Ca^{++} = 1·98 mmol/L), which were treated with blood products and a bolus of 10 mL of 10% calcium gluconate, respectively.

At 6 h, he developed disseminated intravascular coagulation (DIC) with melaena, haemoptysis, haematuria, blood stained naso-gastric aspirate and pulmonary oedema, but associated with an increased haemoglobin concentration (Fig. 1). The haemoglobin concentration rose to 19·8 g/dL despite transfusion of 10 L of crystalloids and colloids. Thereafter, vigorous fluid resuscitation

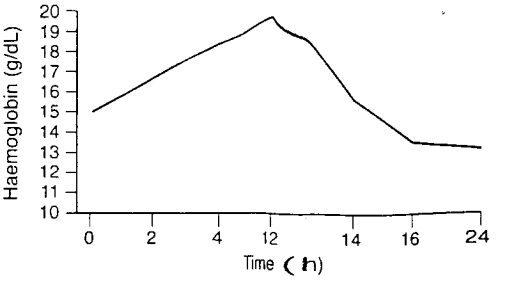

FIGURE 1. *Changes in haemoglobin concentration over the first 24 h of admission to intensive care (range of values: 13·3–19·8 g/dL).*

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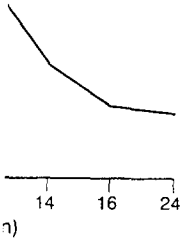

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was continued to a pulmonary capillary wedge pressure of 14 mmHg resulting in a drop in haemoglobin concentration to 13·3 g/dL. He required inotropic support of dobutamine (5–10 μg/kg/min) and an infusion of 10% calcium gluconate, as there was persistent hypocalcaemia (adjusted Ca^{++} = 1·96 mmol/L). These measures increased his cardiac output and raised his blood pressure. Serum CK had risen to 50038 U/L and MDMA and MDA concentrations were 0·29 and 0·01 mg/L, respectively at this time. The pulmonary oedema resolved as the DIC was successfully treated with repeated transfusion of coagulation factors and platelets. Thereafter his cardiovascular system remained stable and he was successfully weaned off inotropic support by day 2. However, he remained deeply unconscious with deranged liver function tests and oliguric acute renal failure. Liver function tests remained deranged until 50 days after admission (Fig. 2), even though the Doppler ultrasonography of splanchnic and hepatic circulations were normal. Acute renal failure (Fig. 3) was managed with daily haemodialysis or haemofiltration until renal function recovered (45th day). To exclude intracranial thrombosis of haemorrhage secondary to dehydration or severe DIC, CT scans of the brain were performed on three occasions. All were normal. Though return of consciousness occurred on the 12th day, he remained dependent on the ventilator. He developed hypercalcaemia (adjusted Ca^{++} 3·15 mmol/L) on the 25th day, which was managed with injections of calcitonin and disodium pamidronate.

The changes in total serum CK activity over 30 days are shown in Fig. 4. The CK-MM isoform pattern was predominantly MM_3, indicating continuous fresh skeletal muscle release even though the total CK activity had fallen significantly to 3040 U/L (Fig. 5*a*). CK-MB was not detected in any of the samples prior to day 26. A sudden increase in CK-MB_2 to MB_1 ratio was observed on day 26 (Fig. 5*b*) associated with pulmonary oedema indicating a myocardial event, but without any ECG changes in the leads monitored (lead II and chest lead V5). Serum total CK activity was measured using a Beckman CX7 analyser (Beckman Instruments, High Wycombe, UK) and the isoform fractions on the Helena REP electrophoresis system using the isoform gels (Helena laboratories, Gateshead, UK).

In view of the difficulty in weaning from the ventilator and persistently high CK activity with predominantly CK-MM_3 (tissue) isoform pattern, electromyography was carried out on the 37th day and showed features of acute muscle necrosis but with well preserved nerve conduction. The reversal of CK-MM_3 to MM_1, ratio after day 30 indicates the normal breakdown pattern of the CK-MM_3 isoform (Fig. 5*c*). He was successfully weaned off the ventilator on the 56th day and discharged to a medical ward on the 60th day. He went home on the 80th day and remained well 1 year later with improved renal function (serum creatinine 185 μmol/L, blood urea 8 mmol/L).

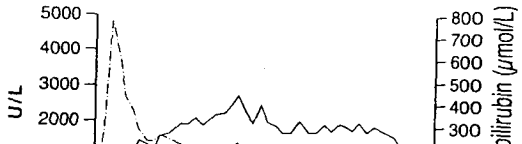

FIGURE 2. *Changes in serum liver function tests. Alkaline phosphatase (▬▬), range of values 84–226 U/L; total bilirubin (——), range of values 17–418 μmol/L; gamma glutamyl transpeptidase (• • • •), range of 28–220 U/L; alanine transaminase (— • —), range of values 25–4600 U/L.*

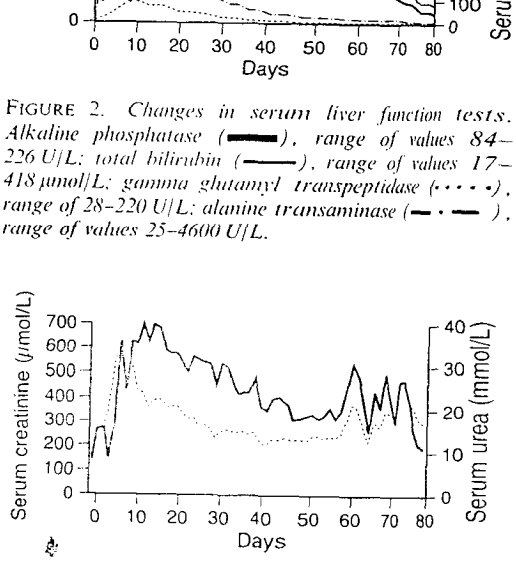

FIGURE 3. *Changes in serum urea and creatinine: urea (——), range of values 4–41 mmol/L; creatinine (• • • •), range of values 120–593 μmol/L.*

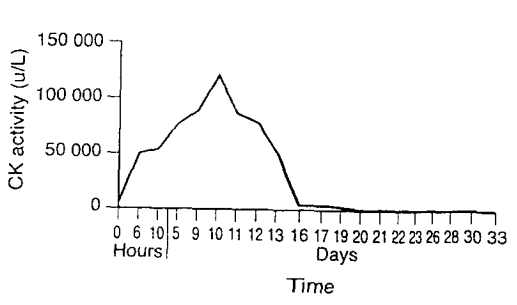

FIGURE 4. *Total creatine kinase activity over 33 days.*

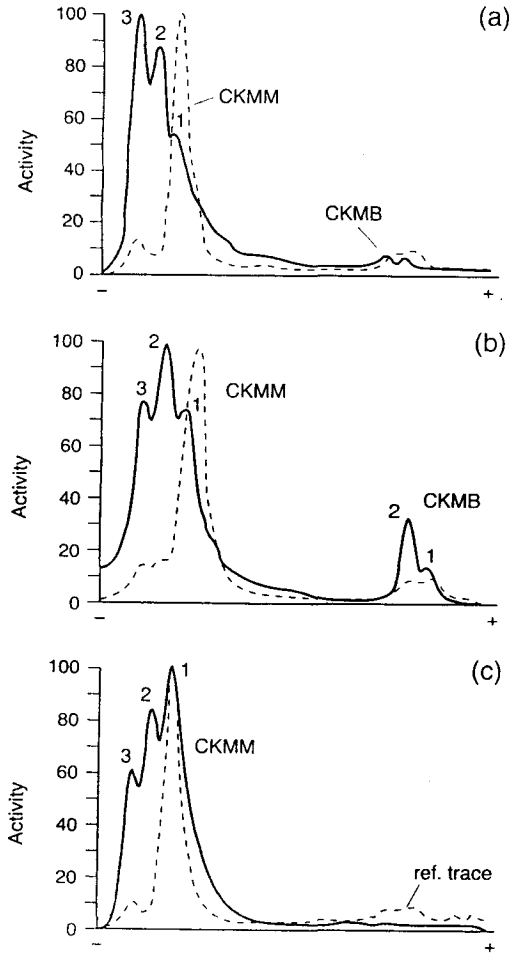

FIGURE 5. *Creatine kinase isoenzyme patterns: (a) Day 19, showing the high CK-MM$_3$ to MM$_1$ ratio (total CK = 3040 U/L). (b) Day 26, showing the high CK-MB$_2$ to MB$_1$ ratio (total CK = 1049 U/L). (c) Day 30, showing the reversal of CK-MM$_3$ to MM$_1$ ratio (total CK = 457 U/L). Activity expressed in arbitrary units.*

DISCUSSION

Ecstasy (MDMA) induces feeling of euphoria, benevolence and enhances sociability. MDMA causes pharmacological alteration in central temperature homeostasis mediated by serotonergic pathways producing hyperpyrexia.[3] At 'rave parties', the euphoric state produced by MDMA overrides the inhibitions leading to continuous physical exertion. The acute toxicity of MDMA is mainly dependent on its pharmacological effect on the brain and associated physical exertion,[1] although abnormalities in drug metabolism in susceptible individuals and other toxic contaminants in the tablets may be important.[4] The various presentations of MDMA toxicity include hyperpyrexia, sweating, dehydration, muscle rigidity, cyanosis, cardiac arrhythmias and cardiac arrest, convulsions, coma, rhabdomyolysis, myoglobinuria, DIC, acute renal failure, impaired liver function, cerebral haemorrhage, cerebral venous thrombosis and psychiatric disturbances.[1,2,5,6]

There is no definitive therapy for ecstasy toxicity except early aggressive supportive therapy by ensuring a patent airway, adequacy of breathing and maintenance of cardiac output. Resuscitation with cold intravenous fluids and aggressive passive cooling are the most important therapeutic interventions in these patients. Initially, our patient's fluid losses (probably into the damaged muscle and gut) were insufficiently recognized as his Hb increased to 19·8 g/dL. This case illustrates the need for vigorous fluid replacement to correct the substantial volume depletion that may occur. The role of dantrolene in ecstasy-induced hyperpyrexia is controversial. Though there is no clear scientific evidence to support its role,[7] the National Poisons Information Service (UK) recommends its early usage in the management of ecstasy toxicity because skeletal muscle contraction is a substantial source of heat production.[8] Dantrolene prevents the hyperpyrexia resulting from increased muscle activity by inhibiting release of calcium from sarcolemma.

Acute renal failure (ARF) associated with ecstasy use may be due to hyperpyrexia, dehydration and hypotension, DIC, rhabdomyolysis and myoglobinuria. Our patient developed reversible ARF which needed haemodialysis and haemofiltration for 45 days. Hyponatraemia, though not seen in this case, is another important presentation of ecstasy intoxication and can be caused by unrestricted intake of water resulting in dilutional hyponatraemia or by inappropriate secretion of antidiuretic hormone provoked by MDMA.[9,10] Cerebral oedema, convulsions and coma can develop as complications of this syndrome.

The hepatotoxicity induced by ecstasy may be due to idiosyncratic toxic hepatitis, thrombotic occlusion of portal or hepatic veins as a result of dehydration, ischaemic or hypoxic injury to the liver or an associated hepatitis. The major derangement of liver enzymes in this case was probably due to toxic hepatitis. Liver transplantation has been attempted for the treatment of fulminant hepatic failure induced by ecstasy

misuse.[1] The initial hypocalcaemia observed in these cases was probably due to metastatic calcification of necrotic muscle, followed by hypercalcaemia in the recovery period due to release of previously precipitated calcium salts.

The rhabdomyolysis associated with ecstasy toxicity usually results in a maximal CK activity over the first couple of days, followed by return to normal.[8,10] The maximal total CK activity of 122,341 U/L on day 10 in this case is the highest ever recorded in a case of ecstasy toxicity. Interestingly, even though the total CK activity had peaked, the high CK-MM_3 (tissue form) to CK-MM_1 (serum form) ratio on the 19th day confirmed the process of continuous progressive rhabdomyolysis (Fig. 5*a*), which could explain the need for prolonged ventilation and severe muscle weakness experienced by our patient.

CONCLUSION

Severe MDMA intoxication requires vigorous supportive therapy to anticipate the problems described above. The changes in CK isoenzymes and isoforms are useful as qualitative biochemical markers of persistent rhabdomyolysis following ecstasy use.

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