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Creatine Kinase Isoform Changes Following Ecstasy Overdose

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The recreational use of stimulant drugs such as amphetamines has become popular at "rave parties" or "acid house parties". There have been several reports of Ecstasy or MDMA (3,4 methylenedioxymethamphetamine) misuse in the medical literature with complications and even fatalities[1,2]. We report a patient with Ecstasy overdose, who survived despite severe multiple organ failure and hospitalization for 80 days. The total serum creatine kinase (CK) levels observed were much higher than any case reported so far and the relevance of serum creatine kinase isoenzyme and its isoforms are described.

CASE REPORT

A previously healthy male was admitted to the Accident and Emergency Department after collapsing at a local night club during a "rave party" on his twenty-first birthday. He was reported to have taken at least seven tablets of Ecstasy, 2.0g of amphetamines and alcohol and to have danced continuously prior to his collapse.

On admission he was unconscious (Glasgow coma score 3), hypertonic, sweating profusely and had dilated pupils. He was pyrexic (axillary temperature 41°C), tachypnoeic (42 breaths.min^{-1}), tachycardiac (170 beats.min^{-1}) and hypotensive (BP 85/60 mmHg). Immediate therapy included resuscitation with two litres of cold 0.9% saline intravenously and endotracheal intubation and ventilation prior to transfer to the intensive care unit. Preliminary investigations revealed a haemoglobin concentration of 15.1 g.dl^{-1}, platelets 73 × 10^{9}.l^{-1}, haematocrit 44%; arterial blood gas analysis showed pH 7.44, PCO_2 2.9 kPa, PO_2 20.7 kPa (FiO_2 0.5) and base deficit 6.3 mmol.l^{-1}. Blood urea, electrolytes and coagulation studies were normal, but serum creatine kinase was elevated (6,111 U/l). The National Poisons Unit, London, U.K. confirmed the presence of amphetamines with an MDMA plasma level of 0.75 mg.l^{-1} and methylenedioxyamphetamine (MDA) plasma level of 0.025 mg.l^{-1}.

In the ICU he was sedated with propofol and alfentanil infusions, paralysed with an infusion of atracurium and ventilated. Resuscitation with ice-cold 0.9% saline was continued at 500-1000 ml/hour with a urine output of 200-400 ml.h^{-1}. The hyperpyrexia (42°C) was successfully treated with two doses of dantrolene 120 mg and tepid sponging with ice-cold water. Two hours after admission, when myoglobin was detected in the urine, intravenous infusions of 10% mannitol and sodium bicarbonate 1.4% at a rate of 50-100 ml.h^{-1} (urine pH 6-8) were started. Investigations four hours after admission showed a mild coagulopathy and hypocalcaemia (corrected total calcium 1.98 mmol.l^{-1}), which were treated with fresh frozen plasma and a bolus of 10 ml of 10% calcium gluconate.

After six hours, the MDMA and MDA levels were 0.29 and 0.1 mg.l^{-1} respectively. Disseminated intravascular coagulation (DIC) (prothrombin time 46 sec, APTT 114 sec, platelets 56 × 10^{9}.l^{-1}, FDP 0.24 g.l^{-1}) developed with melaena, haemoptysis, haematuria and blood-stained nasogastric aspirate but associated with an increased haemoglobin (19.8 g.dl^{-1}) and haematocrit (58%). By this time he had received ten litres of crystalloid and colloid and the DIC was treated with blood products and platelet transfusion. Despite an FiO_2 1.0 and PEEP of 10 cm of H_2O, the SpO_2 dropped to 74% with copious blood-stained and froth-filled ventilator tubings. The systolic BP dropped to 80 mmHg and the chest X-ray confirmed pulmonary oedema. A Swan Ganz

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catheter was passed and the initial cardiovascular parameters revealed a cardiac index (CI) 2.1 $l.min^{-1}.m^{-2}$, pulmonary artery occlusion pressure (PAOP) 8 mmHg, systemic vascular resistance (SVR) 1683 $dyn.s.cm^{-5}$. Despite the florid pulmonary oedema, the PAOP was increased to 14 mmHg by volume loading with colloids. Inotropic support was started with dobutamine (5 $\mu g.kg^{-1}.min.^{-1}$) and an infusion of 10% calcium gluconate was also started as there was persistent hypocalcaemia (corrected total calcium 1.96 $mmol.l^{-1}$). These measures increased his cardiac index to 4.5 $l.min^{-1}.m^{-2}$ and BP to 120/70 mmHg and the pulmonary oedema resolved. Thereafter his cardiovascular system remained stable.

By the next day he no longer required inotropic support and was well oxygenated on 0.45 FiO_2. However he remained unconscious and became increasingly jaundiced with oliguric acute renal failure. In view of the profound dehydration and DIC, brain contrast CT scans were done to exclude intracranial thrombosis or haemorrhage. Despite the normal brain CT scans, he did not regain consciousness until the twelfth day and because of profound weakness he remained ventilator-dependent.

The oliguric acute renal failure (blood urea 15.1 $mmol.l^{-1}$ and creatinine 276 $\mu mol.l^{-1}$) was managed with daily haemodialysis or haemofiltration until renal function recovered (day 45). Abnormal liver function tests were persistent for 50 days after admission. Hypercalcaemia (corrected total calcium 3.15 $mmol.l^{-1}$) developed on day 25, which was managed with injections of calcitonin 50 IU for seven days and a single dose of 35 mg disodium pamidrionate. On day 26, he again developed sudden pulmonary oedema with no ECG changes but associated with CK-MB elevation (Figure 2b). In view of severe weakness and difficulty in weaning, limb electromyography was carried out on day 37, showing features consistent with acute muscle necrosis. Nerve conduction studies showed well-preserved motor and sensory conduction. He was finally weaned off the ventilator on day 56 and discharged from the intensive care unit on day 60.

Total serum CK activity measured on the Beckman CX7 analyzer (Beckman, High Wycombe, U.K.) continued to rise and reached a peak of 122,341 U/l on day 10, only falling below 1000 U/l 26 days after admission (Figure 1) and to a normal value after 45 days. The CK MM isoform pattern measured on the Helena REP electrophoresis system using the isoform gels (Helena Laboratories, Gateshead, U.K.) was predominantly MM_3, indicating continual fresh skeletal muscle enzyme release though the total CK had peaked and was beginning to fall (Figure 2a).

He was discharged home on day 80 with a weight loss of 16kg despite parenteral and enteral feeding, but otherwise well. He has since returned to work and remains well one year later.

DISCUSSION

MDMA is structurally related to methamphetamine and has sympathomimetic and euphoric properties. In rats, MDMA-induced hyperpyrexia is mediated by stimulation of serotonergic pathways and 5-HT receptors[3]. The psychotropic euphoric state produced by MDMA appears to override the normal inhibitions leading to excessive physical exertion. Plasma MDMA concentrations after recreational use are usually about 0.2 $mg.l^{-1}$, but concentrations below this may be associated with serious toxicity if accompanied by sustained physical exercise. Thus acute toxicity will be compounded by intense physical exertion leading to excessive heat production, hyperthermia, heat exhaustion and dehydration. Features of intoxication include agitation, tachycardia, hyper-

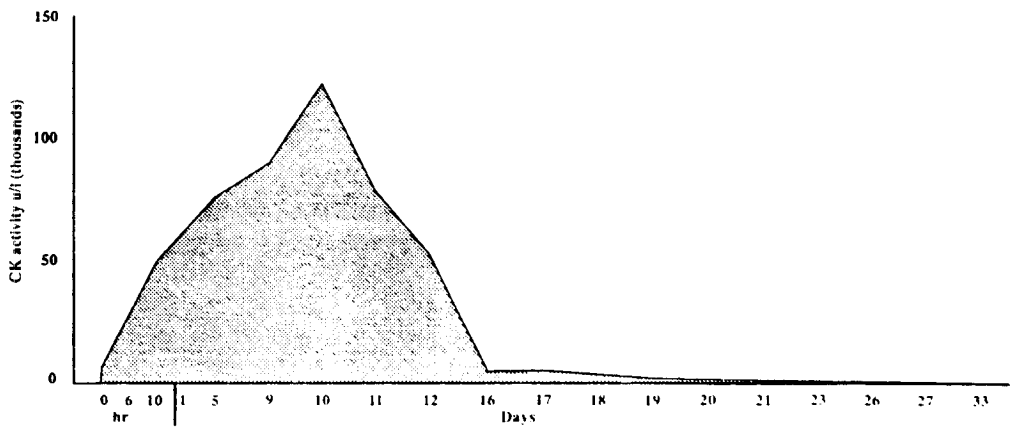

FIGURE 1: Serum creatine kinase (total activity) profile over 33 days.

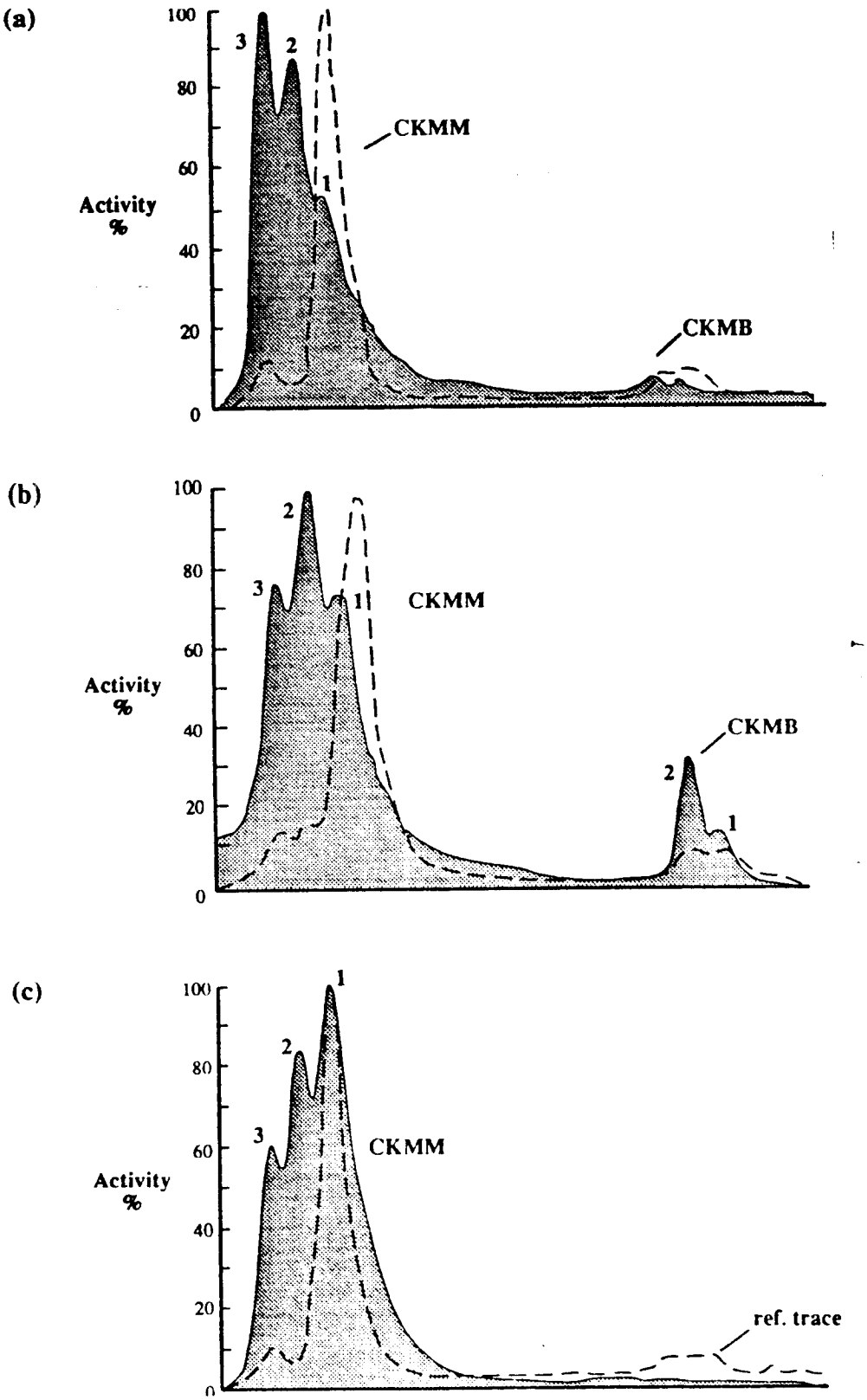

FIGURE 2: (a) CK isoform profile on day 19 showing high CK-MM_3 to CK-MM_1 ratio indicating fresh CK release. (Total activity 3040 U/l.). (b) CK isoform profile on day 26 showing the increase in CK-MB_2 fraction, indicating a myocardial event. (Total activity 1049 U/l.). (c) CK isoform profile on day 30 showing high CK-MM_1 to CK-MM_3 ratio indicating cessation of CK release and a typical breakdown pattern of the CK-MM isoform. (Total activity 457 U/l.)

tension, dilated pupils, muscle rigidity, trismus, sweating, hyperthermia, dehydration, hypotension, tachypnoea, cyanosis, metabolic acidosis, cardiac arrhythmias, cardiac arrest, convulsions, coma, rhabdomyolysis, myoglobinuria, DIC, acute renal failure, impaired liver function, cerebral venous sinus thrombosis, intracranial haemorrhage and psychosis[2,4,5].

There is no specific treatment of MDMA overdose except early and aggressive supportive therapy. Vigorous cooling and fluid replacement are the most critical therapeutic interventions in these patients. Our patient's haemoglobin rose to 19.8 $g.dl^{-1}$ despite transfusion of ten litres of crystalloid and colloid. In retrospect the fluid losses probably into the gut and the damaged muscle were insufficiently recognized. Regular haemoglobin measurements, central venous pressure and perhaps pulmonary artery occlusion pressure are recommended to guide fluid therapy. Although there is no scientific evidence supporting the use of dantrolene[6], the National Poisons Information Service (U.K.) recommends its use in the management of Ecstasy overdose, as skeletal muscle is a substantial source of heat production[7,8]. Alkalinization of the urine reduces renal clearance of amphetamines but prevents renal damage by myoglobin and should be instituted early.

In the literature to date, serum total CK levels (activity) as a consequence of rhabdomyolysis have increased for one to two days and then return to normal[8]. In this case, we observed a peak of total CK activity (122,341 U/l), not only much higher than any other case reported, but occurring on the tenth day indicating progressive muscle damage (Figure 1). This was probably the reason for severe weakness and difficulty in weaning from the ventilator.

The CK isoforms are normal variants of CK-MM and CK-MB isoenzymes with different isoelectric points. Three isoforms of CK-MM and two of CK-MB have been described. $CK\text{-}MM_3$ and $CK\text{-}MB_2$ are the tissue forms, and when released from the tissues, the C-terminal lysine of each M-subunit is cleaved by carboxypeptidase, producing the serum isoforms $CK\text{-}MM_2$, $CK\text{-}MM_1$ and $CK\text{-}MB_1$[9]. The observed high ratio of $CK\text{-}MM_3$ relative to MM_2 and MM_1 indicated continuous CK release for nineteen days, even though total CK had peaked on day 10 (Figure 2a). Later, reversal of the ratio indicates normal breakdown of the $CK\text{-}MM_3$ to $CK\text{-}MM_1$ isoform (Figure 2c). On day 26, CK-MB fraction was markedly increased with a high $CK\text{-}MB_2$ to MB_1 ratio indicating myocardial injury. This could have been due to delayed myocardial necrosis consequent to Ecstasy overdose[10]

The initial hypocalcaemia in these cases is due to metastatic calcification in the necrotic muscle. This hypocalcaemia is followed by hypercalcaemia in the recovery period, due to liberation of calcium salts previously precipitated in the necrotic muscle[11]. Severe hypocalcaemia requires treatment in the presence of cardiac arrhythmias or persistent hypotension associated with low cardiac index and may be life-saving, as in this case. The liver function tests were deranged for 50 days despite normal portal and hepatic circulation as demonstrated by Doppler ultrasonography. This could have been due to idiosyncratic toxic hepatitis, ischaemic or hypoxic liver injury.

In conclusion, MDMA overdose is a medical emergency with a diversity of presentations requiring early aggressive supportive therapy in an intensive care unit. In a case of Ecstasy overdose, clinical management of the patient may be assisted by the analysis of CK-isoenzymes and isoforms as qualitative indicators of continuing rhabdomyolysis.

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