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CASE REPORT

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MDMA induced hyperthermia: report of a fatality and review of current therapy

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Abstract Ingestion of 3,4-methylene dioxymethamphetamine (MDMA), commonly known as "Ecstasy", can produce toxicity that is characterised by hyperthermia, coagulopathy, rhabdomyolysis and renal failure. We report a fatality associated with MDMA ingestion and briefly review the current literature on MDMA-induced hyperthermia.

Key words 3,4-Methylenedioxymethamphetamine · Ecstasy · Hyperthermia

Case history

A 17-year-old male was brought to the emergency room after being thrown out of a nightclub. He had reportedly ingested 10 tablets of Ecstasy and an unknown amount of alcohol. He was delirious and combative, requiring restraint, and was profusely diaphoretic. His axillary temperature was noted to be 41 C, his heart rate was 178 min and his blood pressure was 120/70. His pupils were dilated with minimal response to light. Profound muscular rigidity was noted and noxious stimuli produced a withdrawal response.

Initial management included intravenous saline, general cooling measures with ice packs and soaked sheets, and 1 mg/kg body wt. of dantrolene was given i.v. His level of consciousness progressively declined and respiratory distress developed, requiring immediate intubation and mechanical ventilation with 100% oxygen. Intermittent second-degree atrioventricular block developed, which was transiently responsive to atropine, after which a temporary pacing wire was introduced and the ventricle paced at 100 beats per minute. The patient was transferred to the ICU and hemodynamic monitoring was instituted. Initial laboratory data included K^+ 4.5 mmol/l, bicarbonate 18 mmol/l, urea 4.4 mmol/l, creatinine 143 mic.mol/l and CPK 259 IU/l. Prothrombin time was normal with a platelet count of 404×10^9/l. Arterial blood gases on ambient air revealed pH 7.36, PCO_2 33 mmHg, PO_2 78. *Blood alcohol level was 78 mg/dl. Initial CVP was 17, pulmonary artery pressure 38/22 and PCWP was 21. Cardiac index was estimated at 1.82 l/m² and systemic vascular resistance index at 1086 dyne/m².*

Dantrolene was continued in doses of 1 mg/kg repeated as rapidly as possible, but his axillary temperature increased to 42 C despite a dose of 5 mg/kg body weight (a total of 380 mg of dantrolene). Urine flow could not be established and the patient remained anuric. Evidence of progressive cardiogenic shock was seen with hypotension, pulmonary edema, and declining cardiac output with increasing systemic vascular resistance, which remained resistant to inotropic support. Clinical and laboratory evidence of coagulopathydeveloped with prothrombin and kaolin-cephalin time elevations > 300 s, which was unresponsive to infusions of fresh frozen plasma. Rapidly progressive metabolic acidosis (pH 7.06) developed with hyperkalaemia (K^+ 7.3) that persisted despite repeated doses of sodium bicarbonate, dextrose and insulin. The patient died 6 h after initial presentation.

At autopsy, there was evidence of gross pulmonary edema. The pericardial space was free of blood. There was no evidence of intracranial hemorrhage. Histology of the myocardium revealed a macrophage infiltrate and formation of contraction bands in the muscle sarcoplasma, features that are consistent with *amphetamine abuse* [1, 2]. The blood MDMA level was 0.23 mg/dl and the hepatic content was 1.2 mg/kg of liver tissue. *Apart from ethanol, no other toxins were identified in the body fluids.*

Discussion

MDMA ingestion has been associated with a range of adverse effects that include psychosis, sudden cardiac death, seizures, tachycardia, hepatitis, subarachnoid hemorrhage, and acute renal failure. In a subset of patients, the drug produces an acute syndrome characterized by hyperthermia, coagulopathy, rhabdomyolysis and acute renal failure [3–6]. When fulminant, as in our reported case, death has been the usual outcome [3–5]. Hyperthermia from any cause can lead to rhabdomyolysis, coagulopathy, and multiple organ failure, and its control is of paramount importance in the management of MDMA toxicity. It is an unpredictable complication of MDMA ingestion and is usually associated with vigorous muscular activity such as dancing. MDMA does not have a dose-related effect in humans. A single tablet of "ecstasy", with an MDMA content of 50–150 mg, has resulted in severe hyperthermia and death while the alleged ingestion of 42 tablets, with a resultant plasma MDMA level of 7.72 mg/l, was asymptomatic in one reported case [5]. What predisposes certain individuals to develop hyperthermia following MDMA ingestion is not known. A pre-existing metabolic myopathy or genetic predisposition similar to that seen in patients with

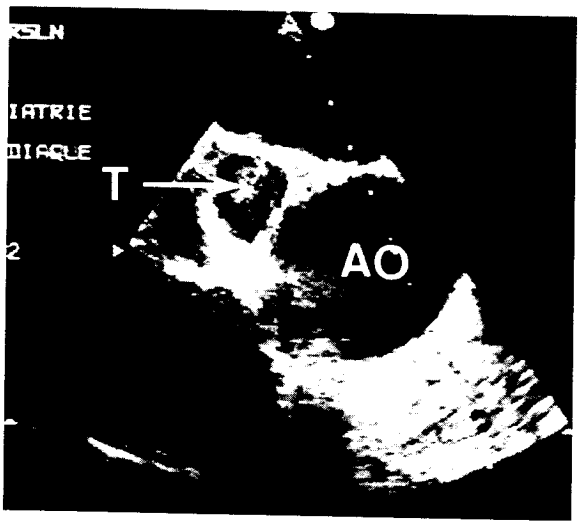

Fig. 1 Visualization by TEE of a nonobstructive thrombus in the superior vena cava with persistent blood flow around the thrombus

been placed for antibiotic therapy and parenteral nutrition. Clinical examination revealed a toxic patient with a blood pressure of 100/50 mmHg, pulse rate of 130 beats/min, and temperature of 40 °C. CVP was 10 cm H_2O. Laboratory results showed a WBC count of 28000/mm^3 and platelet count of 70000/mm^3. The chest X-ray was normal.

Cultures of the central venous catheter tip, blood samples, and Foley catheter were positive for CA. Amphotericin B at 1 mg/kg daily was started, but blood cultures remained positive. To detect the site of CA infection we performed abdominal computed tomography, phlebography of the superior great veins, ultrasonography of the jugular veins, doppler imaging of the lower limbs and transthoracic echocardiography (TTE), which all were negative. A TEE performed with a HP Sonos 1000 5-MHz transducer visualized a thrombus within the SVC extending to the right atrium, without complete obstruction of the vein (Fig. 1).

As no improvement was obtained with the combination of amphotericin B plus low molecular weight heparin, the thrombus was removed surgically. At thoracotomy a thrombus was found partially attached to the vessel wall and almost filling the entire lumen of the right internal jugular vein as far as the right atrium. The infection regressed and resolved 4 weeks later.

TEE is relatively noninvasive and is easily performed compared to other investigations. The possibility of using multiplane transducers and the proximity between the transducer and the SVC allow better visualization of the SVC than does TTE [1]. However, acoustic shadowing by the trachea limits visualization of the more proximal parts, but in many cases SVC thromboses are situated just above the right atrium [2]. This superiority of TEE has already been described by Podolsky et al. [2] and Grote et al. [3]. Our case is an additional example of the inability of TEE to visualize a thrombus in the last 4 cm of the SVC, which could be detected by TEE.

Thrombolytic treatment is not indicated postoperatively, and as the patient was already treated by low molecular weight heparin and amphotericin B without improvement, the clot had to be removed surgically. The surgical concept of venous excision is based on the principle that an endovascular infection behaves as an abscess, in which bactericidal for fungicidal levels of therapeutic agents are unable to reach the focus of infection [4]. We have found four case reports of successful surgical treatment of SVC thrombosis, the most recent one being that by Kelly [5]. Excision combined with amphotericin B cured the CA sepsis in this case.

This case report emphasizes once again the role of TEE in ICU and is an additional report of successful surgical excision of an infected SVC thrombus.

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Severe hypoxia and hypothermia following barbiturate poisoning

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Sir: Hypothermia can be a serious complication of barbiturate poisoning. We observed an intoxicated patient who fully recovered despite concomitant severe hypoxia.

A 50-year-old man (90 kg weight) was found comatose (grade 4) with bilateral mydriasis and rigidity. Systolic blood pressure was 90 mmHg, heart rate 28/min, respiratory rate 4/min. His rectal temperature was measured at 28.5 °C. A right basal pneumonia was evident on chest X-ray. Arterial blood gas analysis showed (FIO_2 0.5): pH 7.27, PaO_2 30 mmHg, O_2Sat 76.8%, $PaCO_2$ 39 mmHg, CO_2t 19 mmol/l and lactate 8.7 mmol/l.

Toxicological analysis revealed a phenobarbital plasma concentration of 112 µg/ml. His core body temperature, determined by the Swan-Ganz catheter, was 30.3 °C and fell to 27.5 °C, 1 h later. The arterial and mixed venous blood samples, which were collected for blood gas determination and for calculation of oxygen-related variables, were not corrected

Table 1 Hemodynamics and oxygen-related values [DO_2 oxygen delivery, VO_2 oxygen consumption, P_{50} PO_2 value at which hemoglobin is half-saturated with oxygen, P_{50} *st* PO_2 value in the standard condition (* calculated from arterial blood in the first sample), *CI* cardiac index, CaO_2 arterial oxygen content, *a-v*DO_2 arteriovenous oxygen content difference, *a-vj*DO_2 arteriovenous (jugular) oxygen content difference, *LOI* lactate-oxygen index]

Delay from admission (h)	5	12	18	22	34
Core temperature (°C)	28.4	32.2	35.2	36.4	38.4
O_2 extraction ratio	0.16	0.20	0.34	0.43	0.21
DO_2 ($ml \cdot min^{-1} \cdot m^{-2}$)	676	459	739	517	627
VO_2 ($ml \cdot min^{-1} \cdot m^{-2}$)	109	94	253	225	134
P_{50} in vivo (mmHg)	16.4*	19.7	24	27	29.8
P_{50} st (mmHg)	10.1*	15.1	29.7	26.1	32.1
CI ($l \cdot min^{-1} \cdot m^{-2}$)	4.03	3.23	4.68	4.5	4.79
Arterial pH	7.34	7.38	7.43	7.48	7.47
PaO_2 (mmHg)	28	45	51	64	119
$PaCO_2$ (mmHg)	48	42	41	44	37
CaO_2 (mmol/l)	16.7	14.2	15.8	11.5	13.1
a-vDO_2 (mmol/l)	2.7	2.9	5.4	5	2.8
a-vjDO_2 (mmol/l)	–	2.5	6.1	4.3	5.7
Cerebral O_2 extraction ratio	–	0.17	0.38	0.28	0.43
Arterial lactate (mmol/l)	2.8	1.0	1.6	1.5	1.6
Jugular bulb lactate (mmol/l)	–	2.1	1.6	1.6	0.9
LOI	–	0.44	0	0.02	−0.12
Plasma phenobarbital (μg/ml)	119	100	103	106	82.5

to the patient's core temperature (Table 1). The Q_{10} is the change in metabolic rate per 10 °C change in temperature and was determined according to the following equation: $Q_{10} = (R_1/R_2)^{10/(T_1-T_2)}$, where R_1 (225 $ml \cdot min^{-1} \cdot m^{-2}$) and R_2 (109 $ml \cdot min^{-1} \cdot m^{-2}$) were the VO_2 values at temperatures T_1 (36.4 °C) and T_2 (28.4 °C) respectively. We found that Q_{10} was 2.47.

The first hemodynamic measurement was obtained 5 h after admission (temperature 28.4 °C), while the patient was receiving low-dose dopamine (333 μg/min). The correction of pH values (using the alpha stat strategy) was achieved within 5 h, without the use of sodium bicarbonate. The PaO_2 value reached only 34 mmHg after 10 h (FIO_2 of 1.0). Passive and active rewarming techniques were applied. Peritoneal lavage was used to enhance phenobarbital elimination and after hemodynamic stabilization, hemoperfusion on activated charcoal was instituted. The patient became responsive to verbal commands within 24 h. Fever developed from day 2 and was related to the bilateral pneumonia. Weaning from mechanical ventilation was achieved on day 15. The patient was discharged on day 25 with an excellent recovery.

We feel that this case illustrates how brain protection against hypoxic damage can occur in the presence of a combination of hypothermia and barbiturates. Little is known about the protective effects of barbiturate therapy in hypoxic hypoxia and hypothermia. In an animal model, the effects of barbiturates and hypothermia on cerebral metabolic rate for oxygen ($CMRO_2$) reduction were found to be additive, but this does not mean that the protective effects were also additive; when used alone, hypothermia was more effective than phenobartital in reducing $CMRO_2$ [1]. Other data show that $CMRO_2$ is unchanged even with PaO_2 values of 35 to 40 mmHg, suggesting that energy metabolism could be maintained within normal limits in the presence of hypoxic brain dysfunction [2]. Moreover, hypoxia may lead to maximal cerebral vasodilation, with cerebral blood flow varying passively with perfusion pressure. In our patient, the cerebral oxygen extraction ratio remained below 0.40. The preservation of cerebral autoregulation is also probably more accurately achieved by using the alpha stat strategy for the management of acid-base disorders during hypothermia [3].

In comparison with the data obtained by Biancolini et al. [4] following active core rewarming in neurologic, hypothermic patients, the values for CaO_2, VO_2, and DO_2 we observed were relatively high, with lower oxygen extraction ratio and P_{50} values. The effect of hypothermia is predictable for VO_2. We found a Q_{10} of 2,47 using VO_2 values at 36.4 and 28.4 °C. The average Q_{10} value reported for many biological systems is 2, corresponding to a 7% change in VO_2 per degree centigrade, and our data indicate that the changes in oxygen consumption were related not only to hypothermia. In contrast, changes in systemic oxygen transport (DO_2) cannot be predicted. Indeed, cardiac output may or may not decrease, depending on sympathetic reflexes or possible alterations in cardiac contractility. Mean arterial pressure and cardiac output were preserved here, despite hypothermia and barbiturate poisoning, either due to an increase in plasma endogenous catecholamine levels or to low-dose dopamine infusion during resuscitation [5]. In addition, CaO_2 may or may nor change, depending on the degree of hypoxia and left shift of the oxyhemoglobin dissociation curve. High CaO_2 values may also have resulted from the initial hemoconcentration. The combination of several favorable factors explains organ protection in this patient.

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