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Case Report :

Malignant hyperpyrexia in an MDMA ("Ecstasy") abuser

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Malignant hyperthermia is a pharmacogenic disease and is manifest by a hypermetabolic crisis with tachycardia, ventricular ectopy, metabolic acidosis, and a rapid rise in body temperature. "Ecstasy", 3,4-methylenedioxy-methamphetamine (MDMA), is a semisynthetic amphetamine, the recreational use of which has increased in recent years. Severe reactions to MDMA have been noted in the past, including hyperthermia, rhabdomyolysis and disseminated intravascular coagulation [1]. Reports of overdose with MDMA are rare, but hyperthermia and rhabdomyolysis have been reported in association [2,3,4]. Compounds such as MDMA are thought to cause hyperthermia by a central action at $5HT_2$ receptors [5]. However dantrolene, a muscle relaxant acting peripherally, has been used apparently successfully in the treatment of MDMA overdose [4]. We report a case of acute perioperative increase in temperature, initially diagnosed and treated as malignant hyperpyrexia, in a patient who later emerged to be an "ecstasy" abuser.

CASE REPORT

A 23 year old man was scheduled for internal fixation of a two day old fracture – dislocation of the right ankle. He had suffered no other injury. He had a squint correction when 6 years old and repair of a Mallory-Weiss tear when aged 17. Both anaesthetics were uneventful, employing thiopentone, suxamethonium, pancuronium and halothane. He reported no medications or allergies, consumed 10-20 units of alcohol per week and was a moderate smoker. He was apyrexial, and other vital signs were normal. Physical examination was unremarkable. He was premedicated with temazeparn 20 mg.

On arrival in the anaesthetic room ECG, pulse oximeter and non-invasive blood pressure monitors were applied. An 18 sw gauge intravenous cannula was placed in a vein on the dorsum of the left hand and an intravenous infusion of Hartmann's solution was commenced. Anaesthesia was induced with fentanyl 0.1mg and propofol 150 mg. After induction, a size 4 laryngeal mask (Intavent)

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was inserted and anaesthesia was maintained with 66% nitrous oxide in oxygen and isoflurane 0.5-1.5%, by spontaneous respiration through a Bain breathing system. The patient was moved to the operating theatre where the same monitors were reapplied. A tourniquet was applied to the right thigh. No antibiotics were administered.

Surgery proceeded uneventfully for 45 min with an SaO_2 of 98% and an end-tidal CO_2 of 4.0-4.5%. It was then noticed that the patient's left shoulder was flushed, felt warm and the heart rate increased suddenly from 55 to 90 beats/min. At the same time there was a rapid rise in the end-tidal CO_2 to 8.5%. A nasal temperature probe was inserted which recorded a temperature of 38.9°C. The heart rate then increased to 120 beats/min. There was no cyanosis and the pulse oximeter continued to show a saturation of 98%. Masseter spasm and rigid upper limbs were noted. An arterial blood gas sample revealed pH 7.28, PO_2 17.2 kPa, and PCO_2 8.04 kPa. A presumptive diagnosis of malignant hyperpyrexia was made and treatment commenced.

Isoflurane administration was stopped and the patient was switched to a 'clean' anaesthetic machine and unused Bain breathing system. While dantrolene sodium was prepared, crushed ice and a cooling blanket were applied to the patient and he was sponged with iced water. A tracheal tube and an oesophageal temperature probe were inserted and the patient manually ventilated with 100% oxygen. The temperature continued to rise to 39°C. The Hartmann's solution was replaced with 0.9% saline. A 16 gauge cannula was placed in the left antecubital fossa and a 20 gauge cannula in the right radial artery. Dantrolene sodium 1mg/kg, pancuronium 4 mg, midazolam 10 mg and methylprednisolone 1000mg were administered. In spite of the cooling measures the temperature continued to rise to 39.1°C with a tachycardia of 150 beats/min. A double lumen central venous catheter was inserted through the right internal jugular vein and an ice cold 0.9% saline infusion commenced. A urinary catheter was inserted and 200ml mannitol 10%, was administered to prevent tubular necrosis.

The patient developed severe bronchospasm which responded to 250mg aminophylline by slow intravenous injection. The oesophageal temperature did not rise beyond 39.2°C. Repeat arterial blood gas samples at ten min. intervals showed normal pH. Serum potassium measurements remained slightly raised. Oesophageal temperature gradually decreased to 36.8°C over the next two hours and cooling was stopped at this stage. The patient was transferred to the intensive care unit, sedated with propofol and fentanyl infusions and ventilated overnight. All subsequent measurements of blood urea and electrolyte concentrations, liver function tests, arterial blood gases and clotting status were normal. He remained normothermic and maintained a good urine output over the next 24 hours. All laboratory investigations remained normal. The highest creatine kinase reported in that time was 235 μmol/1. The endotracheal tube was removed the next morning and he was discharged to the orthopaedic ward. He made a full recovery and was discharged home two days later with instructions on follow up. The patient later confessed to regular ecstasy abuse, the most recent episode being two days prior to the day of surgery. No relevant personal or family history was obtained and he was referred to and examined by a neurologist specialising in muscle disease. On his advice, confirmation of malignant hyperpyrexia as a diagnosis was not pursued.

DISCUSSION

Malignant hyperpyrexia is a rare, potentially fatal condition well recognised in anaesthesia. The true incidence is unknown, with estimates of up to 1:250,000 overall [6]. The primary defect is not known, but is believed to involve an abnormally sensitive calcium-induced calcium release mechanism. As anaesthetists have become more aware of the condition the mortality rate has fallen, but concomitantly the number of dubious and aborted cases has risen. The commoner trigger agents are suxamethonium and halothane, but all volatile agents have been implicated [7,8,9]. Propofol has been studied *in vitro* and *in vivo* and is considered safe [10]. Previous uneventful anaesthesia is not an indicator of nonsusceptibility, even if known trigger agents have been used [8,11].

Malignant hyperpyrexia can be classified into four categories: the fulminant form, abortive malignant hyperpyrexia, masseter spasm and atypical presentations. The clinical diagnosis of malignant hyperpyrexia, especially when made early in the course of the crisis, can be difficult as the signs are non-specific at this stage and other conditions can mimic it to a certain extent. Muscle rigidity may or may not be present, and the predictive value of the most informative signs, when combined, is only 78% specific [12]. Though an increase in temperature of 1°C/hour is quoted as one of the diagnostic criteria in malignant hyperpyrexia, it may well be much faster [8]. An increase in temperature is a relatively late sign, so capnography is of crucial importance at an early stage [13]. Hyoglobinuria and elevated serum creatine kinase are also indicative of malignant hyperpyrexia [12].

Dantrolene, a drug which impairs calcium release from skeletal muscle sarcoplasmic reticulum, is recommended for treatment. It has also been used in the treatment of hypermetabolic states associated with theophylline overdose, the neuroleptic malignant syndrome, exertional heat-stroke, tetanus, toxic reactions to, γ-asperaginase, amphoteracin-B induced rigors and delirium tremers [14, 15, 16]. It has been employed in the treatment of massive MDMA overdose [4].

In recent years the recreational use of the semisynthetic amphetamine, "ecstasy" has increased. Preparations of this substance may contain relatively pure methylene dioxyamphetamine (MDA, "Eve") or its N-methyl cogener MDMA, and biotransformation of MDMA to MDA may occur [17]. Clinically, MDA has been evaluated as an anorectic and antidepressant and as an adjunct to psychotherapy, though it has yet to find an acceptable place in the medical pharmacopoeia [18, 19]. MDA has been shown to be neurotoxic, destroying serotoninergic nerve terminals in the brain [19]. These substances induce a state of excitation of the central nervous system, with central autonomic hyperactivity, manifest as changes in mood (usually euphoric, sometimes depressive) and perception. Trismus, myalgia, tachycardia, hypertension and hyperthermia have been reported [20,21]. Studies in animals have shown MDA toxicity to parallel that of amphetamines and to produce mydriasis, profuse salivation, tachycardia, hypertension, hyperthermia, convulsions and death [19]. These signs can develop several hours after Ecstasy ingestion; the prolonged duration of sympathomimetic action relates to the resistance of these substances to degradation by enzymes that metabolise catecholamines [22]. The unpredictable hyperthermic response to MDA or MDMA in certain individuals may reflect an

underlying metabolic myopathy, with deregulation of mycoplasmic calcium ion homeostasis [23]. The mechanism may involve a combination of direct effects of the drugs and a raised metabolic rate, dehydration or any cause of stress [21].

The cause of the sudden increase in temperature in this case remains uncertain. Initially the clinical impression was of a fulminant malignant hyperpyrexia, though the lack of progression suggested this not to be the case. It may have been an aborted or atypical form of malignant hyperpyrexia, though in view of the normal postoperative serum creative kinase concentration this is unlikely. It may have been a delayed hyperthermic response to the MDMA alone, and purely coincidental with the hospital admission. As the interval between the last ingestion of "Ecstasy" and surgery was less than 48 hours it may have been a result of a combination of residual MDMA, due to its slow metabolism, and a combined factor of hospital admission, surgical stress, catecholamine release and the administration of anaesthetic drugs. A MDMA-induced Ca^{++} release myopathy leading to a deregulation of mycoplasmic calcium ion homeostasis would also be an explanation: as the final common pathway in the development of malignant hyperpyrexia is excessive mycoplasmic Ca^{++}, and hyperthermia with MDMA in certain individuals may reflect a deregulation of mycoplasmic calcium ion homeostasis, this case may represent an additional type of malignant hyperpyrexia.

The differential diagnosis of severe hyperthermia should include 3,4 methylenedioxymetamphetamine intoxication, and serum MDMA concentrations should be measured in young adults who develop hyperthermia during anaesthesia [21, 22]. With the increasing abuse of MDMA and related compounds, the preoperative interrogation of the patient regarding recreational drug abuse should assume greater importance.

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