Ecstasy overdose: a case study

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INTRODUCTION

Ecstasy, 3,4-methylenedioxymethamphetamine (MDMA), is a recreational drug that has become increasingly popular in the UK over the last 4 years. Part of this popularity may lie in laymen's mistaken belief that MDMA is relatively harmless. Unfortunately, this is a fallacy and the increased popularity of the drug has been matched by a concomitant rise in MDMA-related hospital admissions and fatalities.

The treatment of MDMA overdose is a subject of speculation and controversy. Fulminant hyperthermia is an increasingly common symptom seen on presentation which, in some cases, may respond positively to treatment with intravenous Dantrolene (dantrolene sodium) and conventional active cooling. This case study includes examination of the treatment of just such a case of MDMA overdosage and discussion of various aspects of this topic.

CASE HISTORY

A 24-year-old man was admitted to an accident and emergency department after collapsing at a nightclub 'rave'. Inquiries revealed that he had taken 25 tablets of MDMA approximately 1 h before he collapsed. On presentation at hospital he was noted to be profoundly agitated and aggressive. Significant findings on examination included a core temperature of 38.3°C, a sinus tachycardia of 160 beats per min, and a blood pressure of 90/50 mmHg. Arterial blood gases were drawn and showed: pH 7.12, PaO_2 7.0 kPa, $PaCO_2$ 6.2 kPa, HCO^3 16.0 mmol/l and a base deficit of 12 mmol/l.

Initial management comprised high flow oxygen, intravenous Diazemuls (diazepam) and sodium bicarbonate. Despite these interventions his temperature rose rapidly to a peak of 41.2°C. He then was administered intravenous Dantrolene to a total of 120 mg, and was sedated, paralysed, intubated and mechanically ventilated. Active cooling was initiated with topical ice, and intravenous Mannitol and crystalloid were infused to maintain a diuresis. The patient was then promptly transferred to the intensive care unit (ICU) for further management.

Further management included another 20 gm of mannitol to support diuresis and, since his hyperthermia proved to be remarkably persistent, further doses of Dantrolene to a total of 280 mg. Application of topical ice was continued. Hyperkalaemia soon became evident and was successfully treated with intravenous insulin and dextrose. Activated charcoal was instilled into his stomach via a nasogastric tube.

Within 4 h of admission his core temperature had fallen to 36.3°C. 18 h after admission this had risen to 39.5°C, but was responsive to ice application alone and no further doses of Dantrolene were required. Within 36 h of admission his temperature, serum potassium and arterial blood gases had returned to normal and he was extubated and discharged to a medical high dependency unit. Creatinine kinase was noted to be 127 U/l on admission and 1500 U/l on discharge. Remarkably, no significant coagulopathy was noted throughout and his urine test revealed no blood or myoglobin.

DISCUSSION

History and incidence

In 1914 the E. Merck Company patented 3,4-methylenedioxymethamphetamine, a synthetic amphetamine derivative, as an appetite suppressant. In later years its psychotherapeutic use was explored in such areas as marriage guidance, alcoholism and enhancement of perception in the elderly, mostly without success and it lapsed into disuse. Since its major effects are an amphetamine-type stimulation, a feeling of euphoria and benevolence, and enhanced perception it is no surprise that its potential for misuse was discovered and exploited from the 1970s onwards. It is now illegally manufactured in huge quantities and sold under its street name of Ecstasy, or 'E'. It has been banned in the USA since 1985 and has been banned in the UK as a class A drug since 1971 (Henry 1992).

By 1990, despite an explosive rise in the popularity of MDMA, only 4 related deaths had been recorded in the USA, and none in the UK (Chadwick et al 1991). By mid 1991, 7 fatalities in the UK were directly related to MDMA use and inquiries to the National Poisons Information Service in London about MDMA had nearly tripled (Henry et al 1992).

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At present it seems these figures have risen further, judging by the number of Ecstasy-related deaths reported in the media on a seemingly regular basis.

Overdosage and side-effects

The side-effects of MDMA range from mild to severe and fatal. Since the drug is illegally produced, tablet dosages vary, but it is generally thought that each tablet contains 50–150 mg of MDMA. Fatal incidence has been reported with ingestion of a single tablet (serum MDMA 0.424 mg/l) and virtually no side-effects other than tachycardia and hypertension after ingestion of 42 tablets (serum MDMA 7.72 mg/l; Henry 1992). Consequently, there is no firm estimate of a point at which overdosage is likely to occur, and the relationship between the dose of MDMA and the production and severity of severe complications is not straightforward (Barrett 1993).

Minor side-effects that have been reported include: trismus; bruxism; nausea; ataxia; sweating; muscle stiffness; paranoia; insomnia; psychosis and depression (Henry 1992). More serious side-effects include: reports of acute hepatitis (Shearman et al 1992); convulsions and cardiac arrythmias (Singarajah & Lavies 1992); and a report of acute renal failure either as a result of a direct toxic effect of MDMA or secondary to disseminated intravascular coagulation and rhabdomyolysis (Fahal et al 1992).

Fulminant hyperthermia is the sequela of most concern and most likely to lead to a disastrous outcome if not circumvented quickly. All reported fatal cases of ecstasy abuse note this as a common factor, with death usually resulting from a clear pattern of fulminant hyperthermia, rhabdomyolysis and disseminated intravascular coagulation (DIC) (Henry et al 1992; Screaton et al 1992).

The precise mechanism of MDMA toxicity is not clear, but it is suggested that what is of importance is the combination of the drug and the circumstances in which it was taken (Barrett 1992). Larner (1993) speculates that certain individuals may have an underlying metabolic myopathy, with deregulation of myoplasmic calcium ion homeostasis triggered by the excessive physical exertion of dance parties.

Essentially, MDMA taken in hyperactive situations triggers an event similar to a malignant hyperthermic episode. In normal conditions, intracellular calcium levels increase with muscular contraction and decrease with relaxation (Wolcott & Donnell 1990). MDMA, through some unknown mechanism, possibly causes intracellular calcium ion increase, with associated muscular contraction, and prevents decrease and relaxation. This results in erratic, uncontrolled, constant muscular contractions that require great amounts of oxygen and produce large volumes of lactic acid (Thomas 1989).

The rapidly increasing aerobic and anaerobic metabolism accenuates further production of carbon dioxide, lactic acid, energy and heat. Core temperature increase may exceed 2°C per hour (Willats & Winter 1992). A profound acidosis will change membrane permeability, resulting in release of calcium, potassium, creatinine phosphokinase and myoglobin from muscle cells (Thomas 1989). Thus, the cardinal features on presentation are likely to be very high temperature, muscular rigidity, profound respiratory and metabolic acidosis and hyperkalaemia (Willats and Winter 1992). At this point, the acidosis and electrolyte disturbances are sufficient to cause fatal cardiac arrythmias (Henry et al 1992).

Should initial treatment fail to circumvent a rise in temperature deterioration of overall condition will quickly follow. Release of thromboplastin due to changes in membrane permeability leads to DIC, and reduced vascular integrity will result in leakage of blood from vessels.

Myoglobin released by breakdown of muscle cells secondary to sustained muscular contraction will result in myoglobinaemia, acute tubular necrosis and acute renal failure. The presence of dark red urine, myoglobinuria, often heralds this deterioration.

Treatment

The presentation of this type of case is an emergency that will require prompt treatment and cohesive teamwork. Thus, immediate medical and nursing objectives will be one and the same.

Fundamentally, patients are treated rather like a case of malignant hyperthermia. On initial presentation, they are highly likely to be extremely agitated and intravenous sedation, such as Diazemuls, may be indicated to facilitate patient management, allow further treatment and ease symptoms.

High flow oxygen via a facemask should be administered immediately and arterial blood gases, serum biochemistry, full blood counts, toxicology, liver function tests, serum creatinine phosphokinase and clotting studies obtained and repeated at regular intervals as an aid to diagnosis and guide to therapy. Central venous access should be established as soon as possible. If the patient is unable to maintain their own airway, is comatose, or arterial blood gases show a profoundly acidotic state, aggressive respiratory therapy should be initiated. Intubation and mechanical ventilation, initially

with 100% oxygen, with a minute volume 2–3 times the norm will help tissue perfusion and reduction of acidosis. Administration of 8.4% sodium bicarbonate may also be indicated as an adjunct to therapy (Willats & Winter 1992).

ECG monitoring should be commenced immediately. Arrhythmias may be caused by acidotic states or electrolyte disturbances, but use of anti-arrhythmics such as lignocaine, cardiac glycosides and calcium should be extremely judicious as they are likely to exacerbate the hyperthermia (Thomas 1989).

Invasive haemodynamic monitoring is indicated and inotropic support may be required. Hyperkalaemia is very likely to develop and this should be treated with dextrose and insulin. A rectal probe should be inserted for continuous core temperature readings and active cooling should be commenced as soon as possible. External means, such as topical ice and cold sponging, can be incorporated initially, and later internal means such as cold intravenous fluids and cold bladder, rectal and stomach lavages (Thomas 1989).

If the patient is intubated and ventilated, an atracurium infusion should be commenced to control muscular rigidity, hypermetabolism and catabolism (Tehan 1993). Commencement of a continuous intravenous sedative will aid patient comfort. Hyperthermia refractory to active cooling and muscle relaxants can be treated with intravenous Dantrolene, 1 mg/kg initially and repeated up to a cumulative dose of 10 mg/kg until symptoms are controlled (Willats & Winter 1992).

A urinary catheter should be inserted and hourly urine output and colour noted. Urine should be tested regularly for the presence of myoglobin and blood. Since acute renal failure secondary to myoglobinurea is a threat and fluid loss due to sweating will be very high, a diuresis of at least 1 ml/kg/h must be maintained with diuretics and intravenous crystalloid (Willats & Winter 1992). Dantrolene is reconstituted in aqueous Mannitol, which will aid diuresis.

Gastric lavage with cold fluid should be performed, both to remove remaining undigested MDMA and as an aid to cooling. A nasogastric tube should be passed and an activated charcoal regime commenced.

Sedation and paralysis should continue during artificial ventilation until the patient's condition is considered stable enough to commence weaning from it. Since DIC can result in cerebral bleeds, neuological observations should be done when practicable, and repeated. All cavities and insertion sites should be monitored for the onset of insidious bleeding.

As soon as their condition is stable enough, patients should be transferred to an ICU for continuing management.

The use of Dantrolene

The first successful use of Dantrolene to treat fulminant hyperthermia triggered by MDMA abuse was reported by Singarajah & Lavies in 1992. Campkin & Davies (1992) also reported its unsuccessful use in a similar case.

In cases of malignant hyperthermia, Dantrolene is thought to prevent increases in myoplasmic calcium and acute catabolism within the muscle cell by interfering with the release of calcium from the sarcoplasmic reticulum to the myoplasm. Therefore, the detrimental changes associated with the crisis may be reversed or attenuated (Walker 1994). Barrett (1992) suggests that is no firm basis for the assertion that Dantrolene will be any more effective than a non-depolarising neuromuscular blocking agent (such as Atracurium) in cases of fulminant hyperthermia triggered by MDMA abuse. Tehan (1993) suggests Dantrolene be used if Atracurium is ineffective, and that it should be administered before the patient's temperature teaches 42°C to circumvent serious sequelae.

CONCLUSION

In this case the patient had a positive outcome and he was discharged from the hospital after 10 days with no residual problems. Others are not so lucky. The acute phase was remarkable for the fact that rapid intervention, and luck, seems to have prevented deterioration and onset of DIC, or renal failure secondary to myoglobinurea, despite a marked rise in serum creatinine phosphokinase.

The admissions of patients with Ecstasy overdose are emergencies requiring rapid intervention to avoid fatal outcomes. With the continued rise in MDMA popularity, these scenarios will become more common. I hope that as more reports are published a standard protocol of treatment will be developed, and mortality significantly reduced.

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