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EDITORIAL

A.R. Bodenham
A. Mallick

New dimensions in toxicology: hyperthermic syndrome following amphetamine derivatives

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A.R. Bodenham (✉)
Intensive Care Unit, The General Infirmary at Leeds,
Great George Street, Leeds LS1 3EX, UK,
FAX: +44(113)2926361; Tel.: +44(113)2926363

A. Mallick
Academic Unit of Anaesthesia, The General Infirmary at Leeds,
Great George Street, Leeds LS1 3EX, UK

In recent years the abuse of sympathomimetic psychostimulants such as cocaine, amphetamines and their analogues – MDMA (Ecstasy) and MDA (Eve) – has increased world-wide, especially in the United States, United Kingdom and Continental Europe. As a result, a new spectrum in toxicology has emerged. The incidence of psychostimulant-related fatalities has also increased. Toxicological screening performed at a university hospital medical centre in the United States during 1986 revealed 10% of a patient population to be positive for cocaine and its metabolites [1]. An additional 10% sample showed evidence of amphetamines and their derivatives [2]. A recent study demonstrated that 57% of violent assault victims and 22% automobile trauma victims presenting to a trauma centre in Philadelphia had urine or blood tests positive for cocaine and/or its metabolites [3]. A variety of potentially lethal effects of psychostimulants are increasingly encountered in various accident and emergency (A&E) departments. It has therefore become increasingly important for emergency physicians, anaesthesists and intensivists to understand these toxic effects and their management.

Commonly encountered acute toxic effects of psychostimulants include hyperthermia, metabolic derangements, seizures, hypertensive crises, cardiac dysrhythmias, cerebrovascular accidents and complications from other end-organ vasospasm. Complications escalate in severity and number if not treated promptly. These complications include rhabdomyolysis, disseminated intravascular coagulation, adult respiratory distress syndrome and acute renal failure. Biochemical investigations reveal metabolic acidosis, rises in creatine phosphokinase and hyperkalaemia. These complications appear to be related to the duration and degree of hyperthermia. Hyperthermia has been suggested to be contributory in a significant percentage of deaths among amphetamine users in Ontario [4]. Hyperthermia above 40 °C was recorded in all deaths due to MDMA reported to the National Poisons Information Service in London between 1990 and 1995 [5]. Hyperthermia is also associated with severe cocaine overdose and a rectal temperature of 45.6 °C has been reported following acute cocaine poisoning [6].

The case reported by Hall and colleagues in this issue of *Intensive Care Medicine* (p. 671) represents a typical presentation following MDMA use. Toxic effects after MDMA have been less frequently reported in Europe and the United States, where the drug is widely used. To date 53 deaths have been reported in the United Kingdom. It has been suggested that impurities associated with the drug may be responsible for the high fatality rate in the United Kingdom and for the increasingly reported hepatotoxicity. Dehydration as a result of strenuous dancing was thought to precipitate the MDMA-induced hyperthermia. Subsequently there have been reports of deaths caused by dilutional hyponatraemia and acute water intoxication due to intake of excessively large volumes of water following MDMA ingestion. Advice from drug misuse agencies has been to drink water throughout the evening at "rave" parties. Three deaths have been caused by hyponatraemia and other CNS disturbances have also been reported in association with a low serum sodium concentration [7]. Blood-stained profuse diarrhoea is a feature in some patients and is presumably due to ischaemic colitis.

The exact sequence of events which trigger hyperthermia following MDMA is unknown [8]. Individuals who present with such an adverse reaction have often used the drug previously without problems. A batch of the drug is often shared by many individuals, but only one may develop the reaction. Genetic predisposition may be a possible factor [9]. Initially it was thought people who developed this hyperthermic reaction might be susceptible to malignant hyperpyrexia, but in vitro muscle testing has not substantiated this hypothesis [10]. It appears that the severity of adverse effects appears unrelated to the quantity of MDMA ingested [8]. It is unknown whether susceptibility to hyperthermia is increased after a previous reaction.

Hyperthermia is a common feature of severe psychostimulant poisoning and may be the primary mechanism of death in some patients. It has been found in various clinical reports and in animal studies that hyperthermia is a primary effect of psychostimulant drugs and can occur independently of convulsions and increased motor activities. Furthermore, activation of central dopamine and 5-hydroxytryptamine receptors (5-HT_2) appears to be responsible for this psychostimulant-induced hyperthermia [11]. This may be similar to the neuroleptic malignant syndrome [12], which follows exposure to phenothiazines and other neuroleptic agents, or the serotonin syndrome [13], which is increasingly reported with overdoses of newer antidepressants such as selective serotonin re-uptake inhibitors. The combined serotonin-releasing and dopamine-releasing properties of MDMA and MDA may be synergistic in producing hyperthermia [11]. Drug-induced peripheral release of catecholamines may stimulate the muscle and other thermogenic tissues and appears to contribute to hyperthermia [14].

The differential diagnosis of hyperthermic syndromes will depend on geographic factors and the drug habits of the local population. The following should be considered:

1. Heat stroke
2. Neuroleptic malignant syndrome – neuroleptic drugs
3. Serotonin syndrome – antidepressant combinations
4. Malignant hyperpyrexia – anaesthetic volatile agents, suxamethonium
5. Overdose – anticholinergics, salicylates
6. Adverse reaction – amphetamine and analogues, cocaine
7. Severe sepsis/infection.

There is no available antidote for the management of these toxic reactions. Intensive supportive therapy starting in the A&E department and continuing in the intensive care unit is essential. Cardiopulmonary resuscitation is the first priority in patients presenting with apnoea, arrhythmia or cardiac arrest. Seizures or severe agitation require prompt treatment with anticonvulsants such as benzodiazepines. Severe cases will require tracheal intubation, mechanical ventilation and muscle paralysis. Aggressive intravenous fluid therapy with close monitoring of central venous pressure or pulmonary artery occlusion pressure and urinary output are indicated. Rapid and aggressive control of hyperthermia as measured by core temperature is a significant step in preventing mortality and further morbidity. MDMA-induced hyperthermia may be impossible to control with external cooling measures, which may lead to peripheral vasoconstriction and a raised core temperature. Intravenous dantrolene should be administered when the core temperature is above 39 °C and rapidly rising. Rapid control of temperature may prevent or minimise rhabdomyolysis and subsequent myoglobinuria, renal shutdown and hyperkalaemia.

Although no controlled clinical studies of dantrolene for psychostimulant overdoses have been reported, the use of dantrolene to control MDMA-induced hyperthermia is supported by anecdotal reports from other centres [15] and by our own clinical experience. Although dantrolene has been found to be successful in rapid control of temperature in many case reports, its mechanism of action in this condition is unclear. Controlled studies of the use of dantrolene are likely to be difficult due to the small number of patients presenting to many different A&E departments. The only significant side-effect of dantrolene is muscle weakness, which is unimportant in patients already receiving assisted ventilation. Hence early administration of dantrolene can safely be considered. Consideration should be given to stocking dantrolene in A&E departments. In many centres the frequency of MDMA-related hyperthermic reactions now means that dantrolene is more likely to be used for this indication than for malignant hyperthermia.

In summary, hyperthermic syndrome is a potentially lethal but treatable manifestation of psychostimulant abuse. This is a medical emergency and can be severe enough to lead to multiple organ dysfunction and death. Rapid interventions to lower body temperature should improve the chances of survival.

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K.K. Gun
R.E. From

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K.K. Guntupa
Department of
Critical Care M
Baylor College
Houston, Texas

R.E. Fromm, J
Department of
Baylor College
Houston, Texas

Mailing address:
Pulmonary/Cr
Medical Intensi
Ben Taub Gene
1504 Taub Loop
USA

Introduction

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