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CASE REPORT

Sudden cardiac death in excited delirium, and how to prevent it

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Abstract

The purpose of this study was to review data on restraint related deaths in persons in a state of excited delirium (ExDS) and to propose guidelines for treatment. We analysed three unexpected deaths in persons in a state of ExDS shortly after police restraint. Death which occurs during a police intervention, using physical restraints, may be related to placing the individual in a prone position, the use of neck holds, expert grips, and handcuffs or pepper spray. ExDS results in an altered mental state with agitation, aggression, paranoia, and panic attacks, and is a life-threatening condition. Therefore, before police intervention is initiated, a medical emergency team should be present. In patients with ExDS, physical restraints used by the police should be brief, effective, and include rapid tranquilization (sedation) using benzodiazepines, and antipsychotics.

Keywords

Cocaine; Dopamine receptors; Delirium; Hyperthermia; Resuscitation

1. Introduction

Excited delirium syndrome (ExDS) is defined as acute exhaustive mania and is associated with severe psychomotor agitation, violence, unexpected strength, hallucinations, and paranoia. Hyperthermia, rhabdomyolysis, high blood potassium, metabolic acidosis, cardiovascular and autonomic collapse are symptoms of this life-threating condition [1]. People in a state of ExDS are in an altered mental state with agitation, aggression, paranoia, and panic attacks and are therefore very difficult for police to restrain [2]. When death occurs during a police intervention, a number of questions arise regarding the cause of death, especially when police place the individual in a prone position and use chokeholds, expert grips, handcuffs or pepper spray [3–5]. Three unexpected deaths in restrained persons with ExDS were analysed. Pepper spray in combination with cocaine intoxication may enhance delirium symptoms because of their synergistic stimulation on dopamine release [6–8].

2. Case presentations

The authors collected data from law enforcement, prosecution, emergency medical staff, coroners, toxicologists and forensic pathologists and present three unexpected deaths during physical restraint with the use of pepper spray in persons in a state of ExDS (Table 1). The local Ethical Board approved the case presentations, granting waiver of informed consent.

2.1 Case 1

A 31-year-old male sought police help in a state of panic. Prior to the intervention he called the emergency number five times. He kept repeating that he was being persecuted by people with rapid and confused speech, although his sister was trying to convince him that no one was there. He informed the police that he had taken cocaine and ecstasy. When police officers arrived, the man was waiting for them in the yard, diaphoretic, upset and paranoid. He aggressively banged on the roof of a police vehicle, then grabbed the emergency lights and tried to rip them off the vehicle. Despite the police officers' warnings, he continued to be aggressive, removing his T-shirt and appearing as if ready to fight. The police officers used pepper spray, a neck hold and handcuffs to restrain him. During the application of these procedures, the man started shaking with epileptic-like seizures and lost consciousness. The emergency medical service was activated. According to the paramedic's medical record, the Emergency Medical Service (EMS) arrived 12 minutes later. On their arrival the patient was unconscious, apneic, cyanotic and pulseless. Immediate resuscitation with continuous chest compressions and ventilation using an Ambu-bag mask with supplemental oxygen at rate of 12 breaths/min was initiated. The first recorded rhythm by AED was non-shockable. An intravenous route was secured and two doses of adrenaline were administered. A mobile intensive care unit (MICU) with an emergency physician on board arrived eleven minutes after the paramedics. The first recorded rhythm was asystole and severe swelling of the larynx was noted. Intubation attempts failed and a cricothyrotomy using a commercial set was performed to

TABLE 1. Characteristics of the presented case reports.

Case	Symptoms	Clinical signs	Concentration of drugs in blood	Police procedures	Therapy
1	Aggressive behaviour	Diaphoretic	Cocaine 3.55 mg/L	Pepper spray	Adrenalin 12 mg
	Hallucinations		Benzoylecgonine 10.00 mg/L	Handcuffs	
	Paranoia	Epileptic-like		Neck hold	
	Undressing	seizures			
2	Aggressive behaviour	Diaphoretic	Cocaine positive	Pepper spray	Adrenalin 14 mg
	Hallucinations		Benzoylecgonine positive	Handcuffs	
	Paranoia	Epileptic-like		Neck hold	
	Undressing	seizures			
		Bleeding from nose			
3	Aggressive behaviour	Diaphoretic	N/A	Pepper spray	N/A
	Hallucination	Epileptic-like		Handcuffs	
	Paranoia	seizures			
	Undressing	Cyanosis			

Note: N/A (not available).

secure the airway. The initial end tidal carbon dioxide ($etCO_2$) was 20 mmHg. Mechanical ventilation was set as assisted volume control (A/C) with a tidal volume of 6 mL/kg and a respiratory rate of 10 breaths/min. After twenty minutes of resuscitation, the $etCO_2$ increased to 48 mmHg and pulseless electric activity (PEA) was recorded on the monitor, at which point the patient's condition deteriorated into asystole with ongoing resuscitation. During the cardiopulmonary (CPR) attempts, the patient received 12 mg of adrenaline and 1500 mL of saline. After 50 minutes of CPR, $etCO_2$ of 20 mmHg and asystole, resuscitation efforts were terminated.

The autopsy report revealed no injuries that would explain the cause of death. There were surface abrasions on the wrists of both hands and superficial excoriation wounds on the back of the elbows. Internal examination revealed severe pulmonary oedema, mild to moderate swelling of the tracheal mucosa, and slightly narrowed airways. There were no hemorrhages in the muscles and soft tissues of the neck. Histology confirmed severe pulmonary edema with numerous intra-alveolar macrophages and erythrocytes with massive intra-alveolar hemorrhages. Liver steatosis and hypertrophy of the myocardium with moderate atherosclerotic narrowing of the left coronary artery were also confirmed. Toxicological examination showed a positive result for the presence of cocaine and its metabolite benzoylecgonine in both the blood and urine.

2.2 Case 2

Police officers were notified by parents who feared for their lives because their son, a 29-year-old male, former K4 fighter, was breaking things in their apartment. He immediately attacked police officers on their arrival. He was completely naked, upset, diaphoretic and despite the police officers trying to calm him down, he attacked them again and injured all four of them. During the intervention the police officers used pepper spray, performed a professional neck hold and then successfully handcuffed him. Immediately following these actions, they noticed that the man lost consciousness, started bleeding from his nose, and developed convulsions. They placed him in a lateral position and activated the EMS. Upon the arrival of the paramedics the patient was unconscious, gasping and cyanotic. According to the paramedics' medical record the patient lost his pulse during the initial examination. Immediate resuscitation with continuous chest compressions and ventilation using I-gel with an Ambu-bag with supplemental oxygen at rate of 14 breaths/min was initiated. The first recorded rhythm by AED was non-shockable. An intravenous route was secured and the first dose of adrenaline was given. Eight minutes later an MICU with an emergency physician arrived. The first recorded rhythm was asystole and the patient was intubated. Frothy sputum tinged with blood was aspirated. The initial end tidal carbon dioxide ($etCO_2$) was 22 mmHg, which decreased to 10 mmHg after forty minutes of resuscitation. Mechanical ventilation was set as assisted volume control (A/C) with a tidal volume of 6 mL/kg and a respiratory rate of 12 breaths/min. During the resuscitation (CPR), the patient received 14 mg of adrenaline and 1000 mL of saline. After one hour an $etCO_2$ of 7 mmHg was recorded with persistent asystole. Therefore, the resuscitation was terminated.

External examination of the body revealed blood in both nostrils and in the mouth, dilated pupils, numerous abrasions of the upper extremities, bruises of the thorax and lower extremities and a detached nail of the big toe of the right foot. Microscopic examination revealed mucosal swelling of the large and small airways, severe pulmonary edema with abundant acute intra-alveolar hemorrhage and hyperemia of the lung parenchyma without signs of inflammation. There was left ventricular hypertrophy and a 70% luminal narrowing of the interventricular branch of the left coronary artery, small fatty changes of the liver and severe cerebral edema. Toxicological examination showed a positive result for the presence of cocaine and its metabolite benzoylecgonine, both in the blood and urine.

2.3 Case 3

A 44-year-old male driving his own vehicle collided with a police car, crossed the state border at high speed, then broke through a police blockade on the highway and drove away at a speed of more than 200 km per hour. He was stopped by police at another roadblock. He slapped, kicked, shouted and insulted the officers, during which time he was squirming and extremely agitated. The police officers used pepper spray and handcuffs to restrain him, and he was transported to the hospital to manage his uncontrollable, impulsive behaviour. In the hospital he was calm for a while, but then became aggressive, grew cyanotic and began shaking, followed by a cardiac arrest. The medical team initiated CPR, which was unsuccessful. For 15 years he had suffered from manic depression and schizophrenia. Unfortunately, his medical records were not available to the authors for a detailed analysis of the resuscitation. The autopsy revealed minimal abrasions and bruises and a fracture of the left horn of the hyoid cartilage. Histology confirmed severe pulmonary edema with numerous macrophages, mastocytes and erythrocytes, and massive intra-alveolar hemorrhages. No toxicological examination for psychoactive substances or drugs was performed.

3. Discussion

To date, more than 70 cases of deaths while in custody during restraint directly or indirectly related to exposure to oleoresin capsicum (OC) or pepper spray have been reported in the literature [3–5]. Most of the victims were in a state of ExDS [3]. O'Halloran reported seven deaths in custody that involved the use of OC spray during the arrest process. In four cases, the death was certified as due to ExDS, in one case the cause of death was listed as asphyxia by compression of the neck and chest due to restraint, and the manner of death was listed as homicide. In no case was the use of OC responsible for the onset of death [9]. Steffee *et al*. [10] reported that exposure to OC was associated with sudden death in two individuals with ExDS. Similarly, Granfield *et al*. [4] reported 30 cases of death in custody following OC exposure. Both reviews concluded that OC was not the cause of death in any of the cases, but asphyxia, drug-related factors or natural heart disease were noted. Pollanen *et al*. [11] reported four deaths in custody during restraint associated with ExDS in combination with OC [11, 12]. Cocaine enhances dopaminergic neurotransmission in the brain by blocking dopamine uptake and prolonging the duration of dopamine in the extracellular space [13]. Chronic cocaine users are particularly prone to developing ExDS, because cocaine can also augment dopamine release as a compensatory adaptive mechanism [14]. Cathinones inhibit dopamine and norepinephrine reuptake, while amphetamines and methamphetamine-like cathinones inhibit the uptake of monoamines dopamine, serotonin and epinephrine, and are at the same time a stimulus for their release [15]. ExDS symptoms are mostly caused by excessive dopamine in the synapses of dopaminergic neurons in the central nervous system [14].

Pepper spray is an incapacitating agent extracted from a plant chilli pepper (*Capsicum annuum*) and used for restraint and self-defence [3, 16]. Pepper sprays contain from 0.18% to 1.33% major capsaicinoids [6, 17], with a lethal oral dose in humans being 0.5–5 g/kg [18]. The active ingredient is oily OC which causes immediate and transient local inflammatory response at the site of exposure. Burning pain, itching and redness of the skin, swollen eyelids with blurred vision and lacrimation are the most commonly reported symptoms. When inhaled or ingested OC causes a burning sensation in the nasal and oral mucosa with sore throat, chest tightness and dyspnea. Significant systemic effects are uncommon, with only 2.8% of victims in need of medical assistance, mostly due to associated conditions, such as asthma [10, 19]. The irritating symptoms last from 20 minutes to two hours, and skin rashes, itching and sore throat usually disappear within days [6, 18]. In only one case of a young male without any known illness or misuse of drugs did the use of pepper spray cause ventricular fibrillation [6].

Pepper spray in combination with cocaine use can be a lethal combination, as capsaicin potentiates the effects of cocaine [7]. OC in pepper spray causes neurogenic inflammation and interacts with the Transient Receptor Potential Vanilloid subtype 1 (TRPV1) receptors in dopaminergic neurons, and enhances dopaminergic neurotransmission. Marinelli *et al*. [18] reported in preclinical research that the use of OC increased the activity of dopamine neurons in brain tissue, and that the effects were also concentration dependent. Through these receptors, OC can potentiate the effect of cocaine by blocking reuptake of dopamine [7, 8]. The pathophysiological consequences of cocaine use on the human body are cardiovascular and, psychological changes, along with hyperthermia and damage to other organs [19]. Initially, the body reacts with tachycardia, hypertension and euphoria, but after some time catecholamines are depleted and blood pressure falls [20]. Simultaneously, cocaine blocks cardiac specific sodium channels which slows electrical conduction throughout the heart, resulting in bradycardia. In a short time, a cocaine user progresses from tachycardia with hypertension to bradycardia with hypotension and low cardiac output [21]. Changes in CNS (central nervous system) neurotransmitters, signal molecules and their regulation lead to euphoria and other psychological states [22]. Due to extreme excitation, feelings of endless strength and unrealistic cognition of their surroundings, a user can become extremely physically active, even aggressive, generating increased body heat. Overheating and hyperthermia become dangerous not only because of extensive muscle work but also the body's diminished ability of heat regulation – a direct action of cocaine on the dopamine receptors' up- and down-regulation [21]. Along with extreme physical activity and delusions, cocaine can result in decreased appreciation for pain, causing bruising to the extremities [21]. A high concentration of waste products, protein parts and cellular debris in addition to low perfusion and the direct toxic effect of cocaine are devastating for kidney function [23–25]. Nonselective adrenergic activity and hypoperfusion can cause myocardial ischemia [26], and multisystemic organ failure [21]. Although most patients with ExDS will survive, the mortality is approximately 10% [1]. The mechanism of death in ExDS individuals struggling against restraints remains a topic of debate [27]. Patients in ExDS are often in a state of heavy physical exertion involving antigravity muscles and ex-

tremities before and during the physical restraint generating a metabolic acidosis from high oxygen consumption [28]. Stimulant drugs such as cocaine may promote further metabolic acidosis and impair normal behavioural regulatory responses [27]. Concurrent electrolyte abnormalities predisposing to arrhythmias can occur [1]. Restrictive positioning of combative patients may impede appropriate respiratory compensation for this acidemia [27]. It has been shown that the use of the hobble restraint in the prone position decreases mean forced vital capacity by 39.6%, mean forced expiratory volume by 41%, mean heart rate by 21.3%, and mean cardiac output by 37.4% [29]. Strömmer *et al*. [30] reported that aggressive restraint (i.e., manhandling, handcuffs, and hobble ties) was more common in ExDS and fatal cases. They concluded that a diagnosis of ExDS is far more likely to be associated with both aggressive restraint and death. There is no evidence to support ExDS as a cause of death in the absence of restraint; and a restraint-related asphyxia must be considered a likely cause of the death. Therefore, as recommended by Royal College of Emergency Physicians (RCEM), patient restraint time in ExDS patients should be kept to an absolute minimum - the degree of restraint used must be justifiable, reasonable, for the minimum time necessary and proportional to the situation [31] and followed by aggressive sedation, hydration, monitoring and transport of patients by EMS [1]. The role of EMS personnel is also to increase the awareness of ExDS among medical and law enforcement personnel which would lead to better early recognition and management of ExDS individuals leading to earlier interventions that prevent sudden death. Protocols or guidelines combing law enforcement and EMS efforts to manage these patients should be developed [1].

Persons who are in a life-threatening condition in which they may harm themselves and others need both police attention and appropriate treatment. The initial aim of the management of an individual with ExDS should be the rapid tranquilization (sedation) and minimization of their hyper-exertional state [32]. Therefore, pharmacologic agents should be administered for sedation and prolonged physical restraint should be avoided [32]. Benzodiazepines, antipsychotics, and ketamine have all been suggested as candidate agents to treat ExDS [14, 32, 33]. Benzodiazepines such as lorazepam, diazepam or midazolam bind to gamma aminobutyric acid (GABA) receptors, which are the main inhibitory transmitter in the human brain and can be given intravenously, intramuscularly, intraosseously or even intranasally (midazolam) [32, 33]. Doses of benzodiazepines are typically much higher in ExDS patients than those routinely used in the treatment of agitated or anxious persons. Caution must thus be used, as high doses may cause hypotension and oversedation, with possible synergistic effects if the patient has ingested alcohol or other sedatives [33]. Typical and atypical antipsychotics are also used to treat ExDS. First generation antipsychotics such as haloperidol and droperidol antagonize dopamine in the CNS, and are often used to treat agitation and delirium of psychiatric origin. These medications should be used only with continuous cardiac monitoring because of the risk of QTc interval prolongation degenerating into malignant arrhythmias [32, 33]. Functional *N*-methyl-$_D$-aspartate (NMDA) antagonists produce dose-dependent and significant protection against the convulsant effects, and thus attenuate cocaine-induces convulsions and lethality [34, 35]. Anticonvulsant efficacy is achieved by blockade of both competitive and noncompetitive modulatory sites on the NMDA receptor complex [34]. Ketamine, a dissociative anesthetic that acts as an NMDA receptor antagonist, has shown improved clinical results in controlling patients with agitation in a prehospital environment [36, 37]; but should also only be used with continuous cardiac monitoring by experienced medical personal to avoid malignant arrhythmias and hemodynamic collapse.

Supportive treatment via the administration of intravenous (IV) fluids and cooling measures should be initiated after initial sedation. Patients with ExDS can be dehydrated due to increased fluid loss from hyperthermia, hyperventilation (insensible water loss) and profound sweating (diaphoresis) [32, 33]. Therefore, IV fluid replacement therapy is used in most ExDS patients. In the case of hyperthermia, there are several potential treatment options including external cooling, cooled IV fluids or ice packs applied to the neck, groin or axilla [32, 33]. A high index of suspicion for the development of acidosis, rhabdomyolysis and disseminated intravascular coagulation (DIC) should be maintained during the patient workup [32].

4. Conclusions

ExDS can be triggered by different causes such as psychiatric disorders and stimulant drugs, including cocaine. Since excited delirium is a life-threatening situation, police forces should act promptly to stabilize the situation. The use of excessive force, pepper spray, chokehold and prolonged restraint in prone position with hands and legs cuffed at the back during arrest may result in worse patient outcomes. The presence of a medical emergency team is recommended in such cases, with the goals of quick and safe tranquilization, workup of the patient with regular monitoring of vital signs and releasing the patient from restraints. Each patient should later be examined in an emergency department. National guidelines and recommendations need to be developed and implemented with regard to such situations, and all potential participants must be educated about this medical condition and the recommended actions.

AUTHOR CONTRIBUTIONS

RK has contributed to the conception and design of the work, acquisition, analysis, and interpretation of the data and has substantively revised the drafted work. TČG has contributed substantially to the conception and design of the work, the acquisition and interpretation of the data. MS has contributed to the design of the work, analysis and interpretation of the clinical data and has substantively revised the drafted work. IG has contributed to the design of the work, analysis and interpretation of the clinical data and has substantively revised the drafted work. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

An ethical approval is not required. The ethics committee is from University Medical Centre Maribor. As the paper does not include identification numbers of the patients, neither the figures of the patients, the ethics committee decided that a written application and approval are not required. The ethical committee email is eticna.komisija@ukc-mb.si.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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