

ACUTE INTOXICATION DUE TO DESIGNER DRUG *TALISMAN* — TREATMENT DILEMMA IN PRE-HOSPITAL SETTINGS — CASE REPORT AND REVIEW

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ABSTRACT

Currently, the number of novel psychoactive substances (NPS) has significantly increased. Recent reports on the abuse of synthetic cathinones focus on serious physical and psychological risks resulting from their consumption, thereby emphasising that a growing use of these drugs might constitute an important public health. Case report: A young man presented to the emergency department with acute designer drug intoxication complicated with severe respiratory failure. Why should an emergency physician be aware of this? We observe a growing use of NPS among young people. Further studies describing clinical manifestations of intoxication and toxicity of synthetic cathinones and treatment guidelines are still needed.

KEY WORDS: *Talisman*, designer drug, synthetic cathinones, treatment guidelines

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INTRODUCTION

“Designer drugs”, “legal highs” refer to a wide range of products containing novel psychoactive substances (NPS). Such substances have become of increasing concern around the world. Based on the spectrum of exerted psychoactive effects, NPS can be classified into four basic categories, which are as follows: synthetic cannabinoids (SCs), stimulants, opioid-like compounds and hallucinogenic/dissociative substances (psycholeptics). However, a combination of the adverse effects may be observed due to their different chemical structure. The most common groups are SCs and psychostimulants [1]. These substances are usually sold labelled as “not for human consumption” and to avoid criminal liability, under trivial names, such as “bath salts”, “plant

fertilisers” or “incense”. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) operates the European Union’s “Early Warning System” for NPS, monitoring over 350 NPS. According to the most recent report, 81 NPS were notified for the first time in 2013 [2]. Their use often goes undetected, because routine drug screening may not detect them. Moreover, these substances can be associated with significant toxicity, often due to unpredictable concentrations [1–2]. The increase in the number of NPS recorded on the drug market between 2010 and 2015 in Poland caused a decisive action implemented by Polish government administration resulting in the closure of shops selling “legal highs”. Unfortunately, the effects of such actions were short-lived, since selling NPS mainly through

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the Internet is gradually increasing. According to the reports of the Chief Sanitary Inspectorate, the average intoxication rate in 2015 in Poland was about 18.92 cases/100 000 inhabitants, what gives about 300 cases monthly [3]. In 2015 the Polish Ministry of Health confirmed 75 deaths due to NPS intoxications [4].

The most frequently identified NPS in Poland in 2014 were the following: (1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl) methanone (UR-144), 3-methylomethcathinone (3-MMC) and pentedrone [5]. One of the most common designer drugs is the so-called *Talisman*, sold on Polish and German markets. It is easy to purchase through online shops and the price ranges between € 7–14 [6–7]. *Talisman* is a psychostimulant and contains different NPS, i.e. cocaine-MDMA-mixed cathinones, e.g., mephedrone (4-methylmethcathinone), methylone (3,4-methylenedioxy-methcathinone) and ethylone [3]. Regrettably, there is little information on the pharmacology and pharmacokinetics of NPS and the available data are mainly limited to synthetic cathinones and benzylpiperazine (BZP).

We report a case of acute NPS intoxication after the use of a designer drug known as *Talisman* or *Talisman Thor Hammer*, containing cocaine or MDMA-mixed cathinones. The paper discusses a short review of clinical, pharmacological and current treatment aspects of synthetic cathinones.

CASE REPORT

A 23-year-old man was brought to the emergency department (ED) by paramedics with possible designer drug intoxication. The patient's mother heard him scream and the patient had hallucinations. Then his mother described a seizure-like activity followed by cyanosis, gasping for breath and unresponsiveness. The patient's mother admitted her son had a history of heavy and regular drug abuse. In his room parents found NPS known as *Talisman Thor Hammer*, which can be delivered to the system orally or by insufflation. By the time paramedics arrived, the symptoms had become severe. The patient was lying prone. On physical examination patient's level of consciousness as assessed by the AVPU scale was U (unresponsive) and GCS score was 6. Pupils were mid-positioned and poorly reactive. Pre-hospital heart rate was 150 bpm, respiratory rate 8 breaths/min, sO₂ — 81%, blood pressure (BP) 210/110 mm Hg and glucose level 114 mg/dl. Due

to airway obstruction and seizures, after intravenous administration of weight-based doses of induction agents (midazolam and propofol), endotracheal intubation was performed without complications. The patient required mechanical ventilation, oxygen and i.v. fluids (normal saline). Re-evaluation showed heart rate 80 bpm, sO₂ — 96%, blood pressure 160/80 mm Hg and normal sinus rhythm on ECG. The patient was brought to the ED and then admitted to the Intensive Care Unit (ICU). When admitted to the ICU, the patient was unconscious (GCS score 4). The seizures and spasms persisted and pupils were semi-dilated and unresponsive. In order to exclude brain injury, a brain CT scan was performed. Blood samples were obtained for toxicological analysis. Central line catheter and an arterial cannula were placed, BP was 100/60, CVP 4 cm H₂O. 0.5 mg atropine was administered twice due to bradycardia (< 50 bpm). The spontaneous diuresis was 100 ml per hour, and when diuresis was forced with crystalloids, it increased by over 200 ml per hour. The patient was sedated with midazolam and, within the first 12 hours, additionally with thiopental due to persistent spasms, seizures and psychomotor agitation. Then thiopental was discontinued and in the next six hours when the patient remained stable, midazolam was also discontinued. The patient was extubated after the return of consciousness, but remained occasionally confused. Laboratory findings done within the first 24 hours revealed elevated creatine kinase. Large amounts of fluids were administered to maintain forced diuresis. After three days, when there was no need for mechanical ventilation, the patient was still weak, but conscious and left the hospital against medical advice.

DISCUSSION

Epidemiological data and a route of administration

According to U.S. Drug Enforcement Administration, in 2012 methylone was reported to be the 11th most common hallucinogen within the United States [8]. Furthermore, mephedrone was the most common synthetic cathinone between 2008 and 2010 in the majority of European countries. After a number of fatal intoxications associated with this substance, control measures were taken to minimise this phenomenon [9]. Currently the most commonly detected compounds in Poland are the

following: cathinones 3-MMC, pentedrone and MDPBP, and synthetic cannabinoid UR-144. These five compounds constitute over 75% of all identifications. Users of these drugs tend to be males, either youth or young adults [10]. Cathinones are frequently used on weekend nights at night clubs or discos. Mephedrone is popular among men who have sex with men (MSM), who use the drug solely to facilitate sex. An increased spread of HIV and other sexually transmitted infections is reported in this subpopulation [10]. The most common routes of NPS administration are insufflation (snorting), oral ingestion of capsules or tablets: the substance being diluted with water/juice drink or taken as a powder wrapped in a cigarette paper and swallowed — this is the so-called bombing or hammer method used to consume high doses. Rectal insertion, intravenous/intramuscular injections and smoking were also noted [11–13]. It is reported, that injections of mephedrone resulted in vein blockages with development of skin erosion, localised infections, blisters, spots scabs, gangrenous tissue, blood clots and large holes at overused injecting sites [14–15].

Pharmacokinetics/pharmacology and metabolism of synthetic cathinones

Synthetic cathinones exert their action via increasing synaptic levels of monoamines, i.e. noradrenaline (NA), dopamine (DA), and serotonin (5-HT). It is postulated that these drugs interact with the plasma membrane monoamine transporter proteins: NAT, DAT and SERT, inhibiting reuptake of NA, DA, and 5-HT. Some drugs can also promote the release of DA [16, 17]. The discussed group of NPS may be classified into four groups based on their relative potency to act as SERT, NAT and DAT inhibitors and their action as substrate releasers [16, 17] (Tab.1). Focusing

on the cellular level, mephedrone has been shown to increase Fos expression in the cortex, striatum, and ventral tegmental area of the rat brain, resembling the action of methamphetamine and MDMA in the supraoptic nucleus, which is characteristic of MDMA [18]. Several studies on the metabolism of cathinone derivatives in rats and humans indicate that they undergo complex transformation: N-demethylation to the primary amine, reduction of the keto group to the hydroxyl group, and oxidation of the tolyl moiety to the corresponding alcohol and carboxylic acid [16–18]. The main enzyme responsible for the in vitro phase I metabolism of mephedrone and methylone is cytochrome P 450 2D6 (CYP2D6). Phase I metabolites are eliminated with urine as glucuronide conjugates and sulfate conjugates. CYP2D6 plays an important clinical role in the metabolism of cathinones. Moreover, this enzyme is involved in the metabolism of numerous drugs and xenobiotics and pharmacokinetic interactions between psychostimulants or other compounds are likely to occur. The rate of metabolism and toxicity of NPS may depend on the genetic polymorphism of CYP2D6 [18].

Adverse effects/fatal intoxications

The adverse effects associated with the use of synthetic cathinones include a vast array of symptoms, which can be divided into groups summarised in Table 2 [19, 20]. The highest number of fatal intoxications is reported for mephedrone. In the majority of these cases, the substances were identified *post mortem*. Most of the victims were young males with a previous history of drug abuse. The victims usually died due to cardiac arrest or respiratory failure, and less frequently due to multiorgan failure, disseminated intravascular coagulation, haemorrhages or fatal wounds [13, 15, 19, 20].

Table 1. Synthetic cathinones classified into groups based on inhibition activity

Substance	Activity
Cocaine-MDMA-mixed cathinones e.g. mephedrone, methylone, ethylone, butylone, naphyrone	Non-selective monoamine uptake inhibitors, five times higher affinity for DAT than the affinity for SERT Mephedrone enhances the release of DA
Methamphetamine-like cathinones e.g. cathinone, methcathinone, flephedrone, ethcathinone, 3-fluoromethcathinone	By analogy to amphetamine and methamphetamine they act as preferential catecholamine (DA and NA) uptake inhibitors and with an exception of ethcathinone, DA releasers
MDMA-like cathinones e.g. methedrone and 4-trifluoromethylmethcathinone	Potent NAT and SERT inhibitors with low potency at DAT Release NA and 5-HT
Pyrovalerone-cathinones e.g. pyrovalerone and MDPV	Very potent and selective catecholamine uptake inhibitors, do not evoke the release of monoamines

Table 2. Adverse effects of synthetic cathinones as divided into groups

Group	Symptoms
Cardiovascular	Sinus tachycardia, heart palpitations, chest pain, hypertension, S-T segment changes, cardiac arrest
Cognitive	Confusion, cognitive impairment, mental fatigue, disorientation to name and time, loosening of association
Psychiatric	Irritability, anxiety, panic attacks, lack of motivation, anhedonia, depression, agitation, dysphoria, aggression that progressed to violent or even criminal behaviour, and self-destructive behaviour, suicidal ideation and self-mutilation
Neurological	Disturbed sleep patterns and nightmares, insomnia, tremors, seizures, hyperthermia, mydriasis, blurred vision, paresthesias, bruxism, motor automatisms, headache, dizziness
Perceptual	Paranoid delusion and fever
Haematologic	Disseminated intravascular coagulation, thrombocytopenia, anaemia
Gastrointestinal	Nausea, vomiting, anorexia, abdominal pain
Miscellaneous	Profuse sweating leading to diaphoresis, dry mouth, sore mouth/throat, hyponatremia, hyperkalemia, hyperuricemia, increased serum levels of creatinine and creatinine kinase, metabolic and respiratory acidosis, weight loss after prolonged use

Management protocol of acute intoxications with NPS

There have been no specific treatment guidelines for NPS intoxication as yet. Management of patients consists in their stabilisation combined with supportive and symptomatic care. Renal, muscular, cardiovascular, respiratory and hepatic functions should be monitored [13–15]. Also in pre-hospital settings the procedures of advanced cardiovascular life support should be maintained if needed. Patients with hyperthermia may need serial temperature checks during hospitalisation. Agitation and seizures are treated with benzodiazepines (lorazepam, midazolam), aggression and psychosis usually require the use of antipsychotic drugs. In cases of cardiac arrest or respiratory failure, tracheal intubation and mechanical ventilation are recommended. It is still controversial whether aggressive and violent patients should be sedated. This issue requires further investigation [13–15, 19].

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

To date the exact prevalence of NPS misuse remains underestimated. There is also an urgent need to better understand various compounds of NPS (pharmacodynamics, kinetics, toxicity profile, risk of dependency), and short- and long-term risks to

physical and mental health. Treatment for patients with acute and prolonged exposure to synthetic cathinones is primarily symptomatic. The assessment options should include a drug management plan coupled with psychotherapy. Developing clinical research into addiction and acute poisonings related to NPS should be considered a public health priority.

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