Pediatr Pol 2019; 94 (6): 351–356
DOI: https://doi.org/10.5114/polp.2019.92969
Submitted: 5.11.2019; Accepted: 30.12.2019; Published: 31.12.2019

PEDIATRIA Polska
PISMO POLSKIEGO TOWARZYSTWA PEDIATRYCZNEGO
Polish Journal of PAEDIATRICS
OFFICIAL JOURNAL OF POLISH SOCIETY OF PAEDIATRICS

ORIGINAL PAPER

Atypical profile of intoxication with the mix of new psychoactive substances

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ABSTRACT

Introduction: In recent years an increase in the intake of new psychoactive substances (NPS) has been observed in the Polish adolescent population. Synthetic cathinones are a group of evolving drugs with stimulating, mind-altering effects. We report a case series of intentional intoxication with NPS and its atypical clinical course of poisoning.

Material and methods: This study was approved by the Bioethical Committee of the Medical University of Warsaw (No. AKBE/166/2019). Clinical data of three adolescent patients intoxicated with NPS were admitted to two paediatric hospitals in Warsaw and retrospectively analysed. The composition of the preparation found in the patients was confirmed by the reference forensic laboratory. Analysed data from the medical records included: anthropometry, the route of poisoning, Glasgow Coma Scale (GCS), and Poisoning Severity Score (PSS) assessment, as well as the evaluation of vital signs and biochemistry of the peripheral blood.

Results: All of the patients admitted that they had taken intranasally a designer drug called HEX-EN. The patients had disturbances of consciousness with a minimum of eight points in the Paediatric GCS. Two patients were aggressive. All of them developed hypotension and bradycardia at some point of hospitalisation. Moreover, all the patients had an affected respiratory system and muscle stiffness. Two of them had elevated creatine kinase serum level. Two patients showed features of liver damage. The nervous and muscular systems of all the patients were affected in at least a moderate grade. Toxicological analysis of white powder found on the inside walls of a plastic bag revealed a mix of cathinone derivatives: 3-CMC, N-ethylhexedrone (HEX-EN), synthetic cannabinoids, and caffeine.

Conclusions: In most cases, the side effects of NPS result in consciousness disturbances, seizures, hyperthermia, hypertension, and tachycardia. Due to differences in composition and concentration of active substances contained in NPS products, intoxication symptoms are unpredictable and may require different symptomatic treatment.

KEY WORDS:

adolescents, HEX-EN, designed drugs, N-ethylhexedrone, 3-CMC.

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INTRODUCTION

In the middle of the first decade of the 21st century, novel psychoactive substances (NPS), commonly called legal highs or boosters, appeared on the European drug market. The appearance of the new generations of NPS is not a new phenomenon; however, surprisingly, now the scale is enormous with the number of drugs, their diversity, and availability. In recent years, one new substance has been launched weekly on the market (approximately 60 substances annually) [1].

Users of NPS are mainly young people, under the age of 25 years, usually males [1]. The most frequent reasons for drug use are curiosity, the improvement of mood and psychophysical activity, satisfaction from the effects, the legal status of boosters, and the affordable price. According to the Polish Main Sanitary Office, every year several thousand suspected intoxications with NPS are registered – half of them in the summer season [2].

Regarding the influence of NPS on brain functions, emotions, cognitive processes, behaviour, and perception, the following drug groups are distinguished:
1) synthetic cannabimimetics,
2) psychostimulants,
3) hallucinogenic drugs,
4) opioids,
5) sedatives and hypnotics,
6) others.

In recent years, the most popular NPS have been cannabimimetics and psychostimulants from the group of synthetic cathinones (80%). Synthetic cathinones are derivatives of cathinone, which occurs naturally in the plant Khat (*Catha edulis*). β-cathinones are phenylalkylamine derivatives. The backbone of β-cathinones can be modified by the substitution on the α carbon, the amine group, and the aromatic ring, which gives hundreds of possibilities to create new, active substances [3]. The chemical structure of β-cathinone resembles amphetamine; however, the mechanism of action is similar not only to amphetamine but also to cocaine and 3,4-methylenedioxy methamphetamine (MDMA) [4–6]. The psychostimulant effect of synthetic cathinones is mediated by noradrenaline and dopamine, whereas the empathogenic effect is caused by the elevated serotonin level [5].

According to the molecular mechanism of action, β-cathinones are divided into three groups. The first group of drugs inhibit in a non-selective pattern monoamine reuptake and induce serotonin liberation, acting in the same way as cocaine and MDMA. The second, a methamphetamine-like cathinones group, increases the catecholamines synaptic concentration by the inhibition of reuptake of catecholamines, as well as liberation of dopamine. In contrast, the third group of cathinones inhibits the catecholamine reuptake but does not induce dopamine or any other catecholamine liberation [5].

In 2010, when mephedrone became controlled, mephedrone was replaced by 3-MMC, pentedrone, and the others. N-ethylhexedrone (HEX-EN) was synthesised in 2015 as an answer to the introduction of its direct precursor – hexedrone (β-propyl methcathinone) to the list of controlled substances [7]. According to Polish Main Sanitary Office, HEX-EN together with another three substances: 3-CMC, 4-CMC, and 3-CEC, is one of the five most common substances identified among the designer drugs in Poland [2]. In HEX-EN, substitution of an ethyl group with an amino group of β-propyl methcathinone results in the synthesis of a new, active, previously unnotified substance with a similar mechanism of action [3, 5, 8, 9]. The pharmacology of HEX-EN has not been determined yet. The similarity in structure with α-PHP (cathinone with a pyrrolidine ring) and the range of symptoms observed after its intake seem to place HEX-EN in the third group, i.e. norepinephrine-dopamine reuptake inhibitors [8].

Data concerning 3-CMC (3-chloromethcathinone) are scarce, restricted to biochemical producers' websites and NPS users' forums. According to the sources mentioned before, it was synthesised around 2010 and became a substance of NPS users' interest in 2014 [10–12]. 3-CMC, also known as metaclephedrone or clophedrone, is a non-selective inhibitor of monoamine reuptake and inductor of serotonin release. Structurally, it is a substituted form of methcathinone, which is an N-methyl derivate of cathinone [11].

HEX-EN can be taken via both routes: intranasally and by inhalation, where in the case of 3-CMC, some users admit administering it also per rectum, intramuscularly, or intravenously [9]. The first symptoms of HEX-EN action can be seen after a few minutes, and its core effect period lasts up to 4–5 hours [5, 10, 12]. All β-cathinones penetrate the blood-brain barrier [5]. HEX-EN, as a catecholamine reuptake inhibitor, exerts a stimulating effect on the central nervous system. Symptoms reported by users as especially favourable are: mood lifted up to euphoria, improved focus, suppressed appetite, enhanced sex drive, increased sociability, confidence, empathy, and motivation. However, subjectively positive effects are always accompanied by agitation and other unpleasant symptoms such as vomiting, increased heart rate and blood pressure, sweating, dry mouth, muscle tension, jaw clenching, migraines, anxiety, memory disturbances and memory loss, and depression. An elevated dopamine level leads to temporary psychosis manifesting in delusional thoughts and hallucinations [4, 5, 13–16]. By indirect α- and β-adrenergic receptor stimulation, β-cathinones evoke a number of cardiovascular adverse effects from elevated blood pressure, tachycardia, and arrhythmia to cardiac arrest. Other symptoms hazardous to human health include hyponatraemia, hyperthermia, anaemia, and rhabdomyolysis, which together with liver and kidney failure can lead to death [5, 15, 16].

An increase in serotonin level promoted by 3-CMC is described as a feeling of characteristic empathy and motivation to act. Administration of 3-CMC as a single agent is favoured by users for its euphoric action caused by both serotonin and dopamine [10, 12].

MAB-CHMINACA (ADB-CHMINACA) is one of the synthetic cannabinoids and is usually sold on the Internet in the form of a white powder, which is used for the production of herbal highs formulated for smoking intake (by dissolving it in acetone, then soaking the dried plant in it, and evaporating the solvent). The compounds of the synthetic cannabinoid group strongly interact with cannabinoid receptors and are therefore used as substitutes for Δ-9-tetrahydrocannabinol (THC), the main psychoactive compound contained in cannabis. Users of MAB-CHMINACA reported that the symptoms of its use usually appear during smoking; the peak lasts for 30–45 minutes and ends after about 2–3 hours (sometimes symptoms can last up to six hours). MAB-CHMINACA can also be taken orally – then the time of occurrence of the symptoms increases to 8–15 hours. The most commonly reported symptoms are euphoria, relaxation, mood improvement, increased motivation and creativity, increased appetite, drowsiness, and dry cough (data reported on Internet forums). The side effects of MAB-CHMINACA, seen in cases of poisoning with this substance, include vomiting, convulsions, muscle tremors, aggression, agitation, blurred speech, hypertension, wheezing, respiratory failure, and unconsciousness [17].

Another substance, caffeine, is also used as an admixture for drugs to improve its properties. It is often added to powders containing amphetamine and/or synthetic cathinones. Due to its pharmacology, caffeine stimulates the action of the central nervous system and as such is used for consumption.

DIAGNOSTICS

The recent trend of the appearance of NPS makes it necessary to constantly develop methods for their determination in biological materials. One major challenge is the availability of methods of high sensitivity to detect various chemical substances given in low doses in different types of bio-samples. The structural similarity of NPS and its metabolites makes the analysis problematic – only a few modern techniques are sufficient for a complex analysis.

One of the recently developed, successfully applied methods in the determination of n-ethylhexedrone in blood is liquid chromatography–linear ion trap–mass spectrometry (LC-LIT-MS) [7].

In our case series, a sample of the substance found with one of the patients was examined by means of ultra-high-performance liquid chromatography coupled to triple quadrupole mass spectrometry (UHPLC-QqQ-MS/MS).

There are some urine tests and different screening methods for the detection of cathinones, but most common urinary narcotic tests and widely available screening methods for the detection of psychoactive substances do not currently cover cathinones.

MATERIAL AND METHODS

This study was approved by the Bioethical Committee of the Medical University of Warsaw (No. AKBE/166/2019). Clinical data of three adolescent patients intoxicated with mix of NPSs, admitted to two paediatric hospitals in Warsaw, were retrospectively analysed. The composition of the legal high preparation was confirmed by the reference forensic laboratory, by means of UHPLC-QqQ-MS/MS. The analysed data included: duration of symptoms, anthropometry (age, sex, height, weight, BMI), and the route of administration. Peripheral blood samples were collected from all the patients, and the following biochemical tests were conducted: level of creatinine, creatinine kinase activity, alanine and aspartate transferases activity, troponin level, and sodium and potassium levels. Vital signs such as blood pressure, heart rate, body temperature, and respiratory rate as well as the presence of muscle stiffness, agitation, and aggression were monitored. The patients' consciousness was assessed using the Paediatric Glasgow Coma Scale (PGCS) – the modified Glasgow Coma Scale adjusted for the paediatric population. The level of intoxication was graded with the Poisoning Severity Scale (PSS). The Poisoning Severity Score is a standardised, qualitative scale designed for the assessment of a patient's overall clinical course, including both subjective symptoms and objective sings. The severity is rated from 0 – none, through 1 – minor, 2 – moderate, 3 – severe, to a maximum of 4 – fatal poisoning [18].

RESULTS

Three adolescent patients (two males, median age 16.86 years), admitted to the Department of Pediatrics and Clinical Assessment Unit of Medical University of Warsaw and the Department of Pediatrics of Prof. Jan Bogdanowicz Children's Hospital in Warsaw, due to intoxication with a substance during June 2018, obtained the drug from the same source and were informed that the substance was called HEX-EN.

The composition of a legal high preparation was confirmed by the reference forensic laboratory, by means of UHPLC-QqQ-MS/MS. The mixture contained: 3-CMC, HEX-EN, synthetic cannabinoids (MAB-CHMINACA), and caffeine, but due to the trace amount of material (less than 1 mg of the white powder found on the inside walls of a plastic bag) it was not possible to perform a percentage composition analysis.

In all cases, the drug was taken by nasal route. None of the patients had previous history of any chronic disease affecting cardiovascular, pulmonary, or gastrointestinal systems.

TABLE 1. Clinical evaluation of the intoxicated patients

Characteristics	Laboratory norm	Patient A	Patient B	Patient C
Sex		F	M	M
Age (years)		16.5	17.33	16.75
Weight (kg)		54.4	73	90.5
Height (m)		1.69	1.77	1.75
BMI (kg/m^2)		19.05	23.30	29.55
Max. temperature (°C)		36.9	36.7	38.4
Time of hospitalisation (days)		3	3	9
Route of administration		Intranasal	Intranasal	Intranasal
Minimal GCS points		8	8	10
Aggression		No	Yes	Yes
Min. systolic pressure (mm Hg)		79	97	96
Max. systolic pressure (mm Hg)		130	130	130
Min. diastolic pressure (mm Hg)		39	44	61
Max. diastolic pressure (mm Hg)		70	68	88
Min. heart rate (per minute)		41	38	60
Max. heart rate (per minute)		99	82	102
Min. respiratory rate (per minute)		9	9	25
Max. respiratory rate (per minute)		15	14	25
Creatinine (mg/dl)	0.2–0.7	0.9	0.8	0.88
Creatine kinase (CK) (U/l)	33–145	55	1248	5326
Max. alanine transaminase (ALT) (U/l)	10–40	29	86	103
Max. aspartate transaminase (AST) (U/l)	15–45	16	103	166
Max. highly sensitive troponin (ng/l)	< 19	4	21.8	–
Min. Na (mmol/l)	132	142	142	135
Max. Na (mmol/l)	145	147	145	145
Min. K (mmol/l)	3.5	3.8	4.2	3.9
Max. K (mmol/l)	5.1	4.3	4.6	4.4

The length of hospital stay was from three to nine days, and the symptom lasted for three days in each case. The patients had disturbances of consciousness with a minimum of eight points in the Paediatric Glasgow Coma Scale. Moreover, two patients were aggressive: one only verbally while the other one also physically, and thus he required immobilisation. All of them developed hypotension and bradycardia at some point of hospitalisation: with a minimal systolic pressure of 79 mm Hg, minimal diastolic pressure of 39 mm Hg, and minimal heart rate of 38 beats per minute. Two out of three patients suffered from bradypnea (nine breaths per minute). In all patients, muscle stiffness occurred, while two of them had elevated creatine kinase serum level. Also, two patients showed signs of liver damage (elevated ALT and AST level). One patient had slightly elevated troponin level. None of the patients had marked electrolyte disturbances (Table 1).

All the patients were evaluated with the Poisoning Severity Scale (PSS). Nervous and muscular systems of all the patients were affected in at least moderate grade. Moreover, the respiratory system of all the patients was also affected. Two patients had moderate symptoms of the cardiovascular system and two had minor symptoms of the liver (Table 2).

DISCUSSION

The use of NPS is an emerging problem in Polish society. Patients poisoned with NPS are a challenge for doctors because the effects of these substances are unpredictable for several reasons. First of all, it is a very large group of psychoactive substances, which is constantly growing. In addition, very often legal high preparations are mixtures of various NPS and/or contaminants in unknown concentrations, which can diametrically change symptoms of poisoning, as in the described cases.

The clinical course of poisoning may by similar to the symptoms of metabolic or neurological diseases and

neuroinfections. Thorough medical history is essential, including knowledge about any neurological symptoms, psychomotor development disorders, or laboratory abnormalities that were previously present. Information about diseases occurring in the family may also be helpful. It may be problematic to differentiate poisoning from neuroinfections; therefore, also anamnesis concerning symptoms (e.g. fever, cough, rhinitis), physical examination, and evaluation of laboratory tests, including the markers of inflammation, are crucial. During an interview, the patient and parents should also be asked about the possibility of head trauma, along with a physical examination – computed tomography of the head should be considered.

In the case of a documented consumption of a psychoactive substance or high likelihood of it, it is necessary to report the case to the police. We should also ask parents to search the child's belongings to see if any suspicious substance can be found that could be the cause of poisoning. If the patient with suspected NPS poisoning is admitted to the hospital, a fast urine test for drugs should be performed as one of the first screening tests. It usually detects the following substances: amphetamine, marijuana, ecstasy, and opiates.

The abuse of so-called designer drugs can lead to potentially life-threatening complications, and regarding the fact that NPS are frequently taken together as "cocktails", the effects could be completely opposite to those expected on the basis of a drug name, as in our case series. Cardiovascular complications of "legal highs" may be a manifestation of actions on the peripheral or central nervous system, or both simultaneously. HEX-EN and 3-CMC, as norepinephrine-dopamine reuptake inhibitors, promote activation of the sympathomimetic nervous system. The effects of heightened catecholamine concentration in the synaptic cleft should present as varying degrees of tachycardia, vasoconstriction, unpredictable blood pressure fluctuations, and arrhythmias [19].

In contrast, in our patients we observed a tendency towards psychomotor inhibition, bradycardia, hypotension, and bradypnoea. Due to the differences in composition and concentration of active substances contained in NPS products, intoxication symptoms may differ and require different symptomatic treatment.

A major limitation of this paper is the lack of qualitative and quantitative testing of the biological materials taken from the patients. This should be performed from two sources: blood and urine. Toxicological methods should concentrate on both primary substances and metabolites. Although the results obtained in the case of NPS usually have no significance for treatment (symptomatic), they allow for the initial determination of the course of intoxication, expected reactions, and the scale of symptoms. In practice, this means a faster prediction of the possibility of life-threatening events and referral of the patient to the intensive care unit. The problem is that most hospital laboratories do not carry out advanced toxicological tests to determine NPS. In such situations, it is worth using local forensic toxicology laboratories that can successfully carry out expert analyses.

TABLE 2. Evaluation of Poisoning Severity Score of the intoxicated patients

Effect	Patient A	Patient B	Patient C
GI-tract	0	0	0
Respiratory system	1	1	2
Nervous system	2	3	2
Cardiovascular system	2	2	0
Metabolic balance	0	0	0
Liver	0	1	1
Kidney	0	0	0
Blood	0	0	0
Muscular system	2	2	2
Local effects on skin	0	0	0
Local effects on eye	0	0	0
Local effects from bites and stings	0	0	0
Total	7	9	7

CONCLUSIONS

In most cases, the side effects of NPS psychostimulants (synthetic cathinones) result in consciousness disturbances, seizures, hyperthermia, hypertension, and tachycardia. Our case series of intoxication with a mix of NPS containing 3-CMC, N-ethylhexedrone (HEX-EN) synthetic cannabinoids, and caffeine revealed an unexpected clinical course of poisoning with a tendency to psychomotor inhibition, bradycardia, hypotension, and bradypnea. Due to differences in the composition and concentration of active substances contained in NPS products, intoxication symptoms may differ and require different symptomatic treatment. In all cases, it is necessary to assess the biological materials from patients (blood, urine) in order to determine the concentrations of psychoactive substances.

DISCLOSURE

The authors declare no conflict of interest.

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