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Clinical manifestations and analytical reports for MDPHP acute intoxication cases

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ABSTRACT

MDPHP is a synthetic cathinone (SC) belonging to α-pyrrolidinophenone derivatives. It is a central nervous system stimulant and may induce hallucinations, paranoia, tachycardia, hypertension, chest pain, and rhabdomyolysis. In literature, a few cases of intoxication have been reported. In the present study, 17 cases of MDPHP intake were described including the analytical findings and clinical manifestations. MDPHP was quantified by liquid chromatography–tandem mass spectrometry in blood (range 1.26–73.30 ng/mL) and urine (range 19.31–8769.64 ng/mL) samples. In three cases the presence of α-PHP was observed. In one case, MDPHP was the only detected substance. Concomitant use of MDPHP with other substances, particularly psychostimulants, was common and it was difficult to describe the peculiar clinical characteristics of this SC. Most of the symptoms overlapped those expected, some of them were unusual and all of them particularly severe thus inducing the research of NPS in laboratory tests. We demonstrated the presence of psychiatric, neurological, and respiratory symptoms, as well as the possible presence of rhabdomyolysis and cardiotoxicity associated with the use of MDPHP. ED admissions were also more frequent in patients with addiction problems. In some cases, MDPHP intake required intensive supportive care. A multidisciplinary approach, including specialist consultation, is recommended for patients showing challenging features. Moreover, we demonstrated that the adoption of advanced analytical techniques, i.e., liquid chromatography–tandem mass spectrometry, is necessary to detect these molecules. Further studies are needed to understand MDPHP intake patterns and associated symptoms. It is essential to raise awareness in addiction treatment centers and among potential users, especially young people, and chemsex addicted.

1. Introduction

The persistence of new psychoactive substances (NPS) on the illegal market of drugs of abuse still represents a huge challenge and threat to public health [1–6]. In 2022, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) signalled 41 new compounds and it was monitoring around 930 compounds. Among them, 162 molecules belong to the class of synthetic cathinones (SCs) whose seizures have been increasing in recent years. This increment was mainly due to large-scale seizures of 3-methylmethcathinone (3-MMC), 3-chloromethcathinone (3-CMC), and N-ethylhexedrone [7]. SCs are derivatives of 2-amino-1--phenylpropan-1-one (Fig. 1), or cathinone, a stimulant agent presents in the khat plant (Catha edulis). They are also called "bath salts" as they are commonly encountered as white or brown crystal powder. Ingestion and snorting are the main modes of consumption, but they can also be injected. Injection of SCs has been linked to chemsex practices and an increased risk of HIV and HCV outbreaks [7]. SCs are central nervous system (CNS) stimulants, and the main effects are paranoia,

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hallucinations, increased friendliness (entactogen effect), panic, and agitation. Moreover, these substances can induce tachycardia, hypertension, chest pain, and rhabdomyolysis. Substituents play a key role in the pharmacokinetics and pharmacodynamics profiles. Pyrrolidine moieties increase lipophilicity thus increasing the potency. The most important pyrrolidine derivative (α-pyrrolidinophenone) is the 3, 4-methylenedioxy-pyrovalerone (MDPV). Its mechanism of action has been widely studied and it acts as a stimulant of dopaminergic and noradrenergic systems through a double mechanism: increment of their release and inhibition of reuptake [8–11]. Nevertheless, a recent preclinical study demonstrated that MDPV acts as a potent uptake inhibitor at plasma membrane transporters for dopamine (DAT) and norepinephrine (NET) [12].

Besides MDPV, other α-pyrrolidinophenone have been synthesised and detected, such as the α-pyrrolidinovalerone (α-PVP), α-pyrrolidinohexiophenone (α-PHP), and the 3,4-methylenedioxy-hexanophenone (MDPHP). MDPHP was notified to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for the first time in 2014 and in Italy is a controlled substance since 2014, firstly as analogue of cathinone and then as a single compound in 2020. Its structure is closely related to MDPV causing a similar mechanism of action and effects. However, the longer aliphatic chain than MDPV (4 C vs 3 C), seems to slightly increase the potency in the inhibition of dopamine transporters (DAT) [13]. Currently, only a few cases of intoxication have been reported in literature. Recently, Grapp et al. have described 9 cases of intoxication by concomitant consumption of MDPHP and other psychoactive substances [14]. Other cases have previously been reported by Beck et al. in the frame of the STRIDA project [15]. Moreover, only two cases of death involving MDPHP have been published so far [16,17]. However, little was described about the clinical manifestations and symptoms. In this paper, we focused on peculiar and common clinical features observed in 17 cases of intoxication by MDPHP aiming to provide indications useful for the healthcare personnel.

2. Materials and methods

2.1. Chemicals and reagents

Acetonitrile (ACN) for protein precipitation was purchased from Panreac Quimica S.L.U. (Castellar del Vallès, Spain). Water (H2O) and ACN for LC-MS/MS were acquired from Biosolve Chimie SARL (Dieuze, France). Formic acid was obtained from Merck KGaA (Darmstadt, Germany). 3,4-MDPHP and α-PHP were purchased from Comedical s.r.l. (Trento, Italy) by the Italian Early Warning System and donated to our laboratory. Mephedrone-d3 (internal standard, IS) was supplied by LGC standards (Milan, Italy). All standards were diluted to the appropriate concentration with MeOH.

2.2. Sample treatment

Blood and urine samples were analysed following a previously published method [18]. Briefly, 200 μL of biological fluids were added with the IS and then a protein precipitation was achieved with 600 μL of cold ACN (0 °C). After mixing and centrifugation (5 min, 2500 G), supernatant was then collected and dried under a gentle nitrogen stream (40 °C). The samples were then reconstituted with 100 μL of H_2O and injected into the liquid chromatography-tandem mass (LC-MS/MS) system.

2.2.1. LC-MS/MS

Analysis was conducted using an HPLC Agilent 1290 Infinity system (Agilent Technologies, Palo Alto, CA, USA) interfaced with an Agilent 6460 Triple Quad MS (Agilent Technologies), equipped with an electrospray ion source (ESI) operating in positive mode. The ESI configuration was: gas temperature 325 °C; gas flow rate 10 L/min; nebulizer 20 psi; capillary 4000 V. Two multiple reaction monitoring (MRM) transitions for each compound (Table 1) were used (for the full list of

Table 1
MRM transitions and retention times for MDPHP, α-PHP and mephedrone-d3. In bold the quantitative fragment.

Compound	Fragmentor (V)	$[M+H]^+$	Product ion (*m/z*)	Collision energy (V)	Retention time (min)
MDPHP	113	290	**135**	25	15.6
			140	29	
α-PHP	123	246	**140**	29	14.6
			91	25	
Mephedrone-d3	90	181	**148**	17	7.6
			163	5	

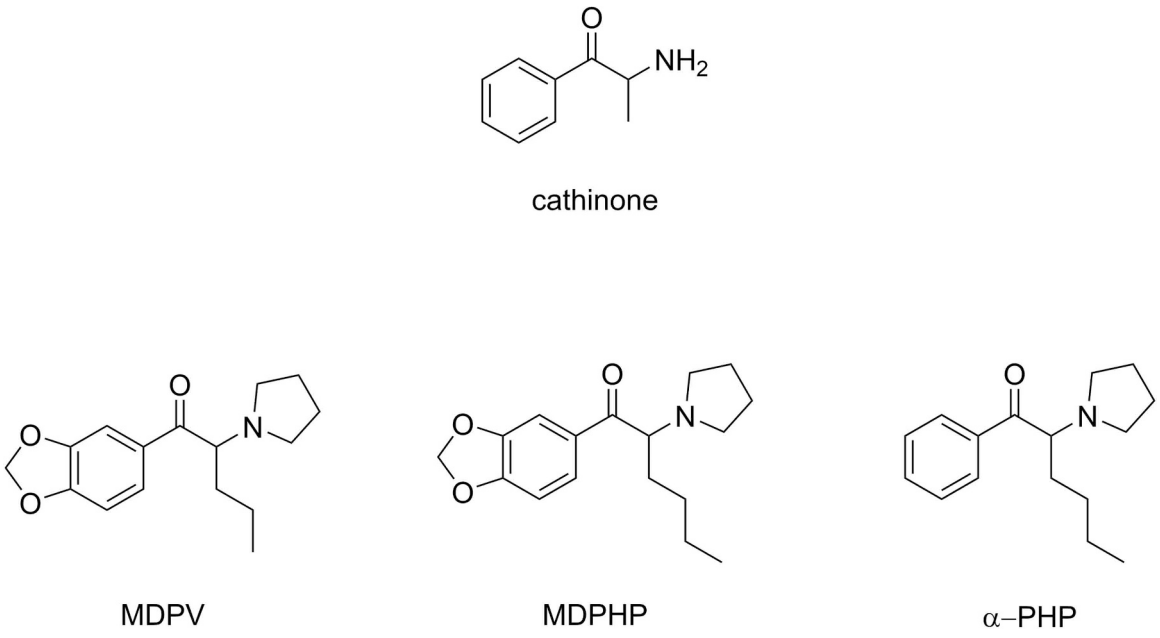

Fig. 1. Chemical structures of cathinone, MDPV, MDPHP and α-PHP.

detectable compounds see previous published paper [19]. Data acquisition and elaboration were performed using the Agilent Mass Hunter Workstation software package. Chromatographic separation was performed through a Zorbax Eclipse Plus C18 (2.1 ×100 mm, 1.8 μm, Agilent Technologies). The mobile phase initially consisted of 5 mM aqueous formic acid (A) and ACN (B) 99:1 (Fig. 2). The gradient of elution was carried out as follows: from 0–5 min, linear ramp from 0–5% B; from 5–7 min, ramp to 10%B; isocratic hold from 7 to 10 min; from 10–15 min, ramp to 20%B; from 15–20 min, ramp to 30%B; isocratic hold up to 22 min; form 22 to 25 min, ramp to 40%B; from 25 to 28 min, ramp to 50%B; from 28 to 30 min, ramp to 70%B; from 30 to 35 min to 100%B and isocratic hold to 37 min. Post-time was set at 2 min. The flow rate was 0.6 mL/min.

2.3. Case series presentation

This study examined information collected about patients who had used MDPHP, assessing various factors such as age, gender, mode of use, time since last use, previous psychiatric history, and presence of neurological, respiratory, or psychiatric symptoms. The occurrence of rhabdomyolysis and cardiotoxicity was also evaluated. Instrumental examinations, duration of hospitalization, patient outcome, and psychiatric counselling performed were also considered. Screening tests on urine samples were routinely performed at admission in case of suspected intoxication. These tests are able to provide qualitative information about the alleged consumption of only the main drugs of abuse (cocaine; Δ9-tetrahydrocannabinol –THC–, opiates/opioids; benzodiazepines; amphetamines; 3,4-methylenedioxymethamphetamine –MDMA–). When clinical manifestations and/or circumstances suggest the use of NPS or unknown substances, as indicated by the Poison Control Centre of Florence, biological samples (whole blood urine and/or hair) are collected and send to the Forensic Toxicology Laboratory of the Careggi University Hospital in Florence where are analysed [18,20,21]. Between January 2022 and September 2023, MDPHP was detected in 14 cases.

According to Italian law, the previous approval by the Local Ethics Committee is not required for this kind of research (e.g., case series). The study was conducted according to ethics principles dictated by the declaration of Helsinki and Oviedo Convention.

3. Results

3.1. Patients' demographics, route of exposure, and symptoms

Since January 2022, 14 cases (eleven different patients) have been found positive for MDPHP. One patient was hospitalised twice and one three times (case #5 in October 2022, and case #5-bis in May 2023; case #1 in January 2022, case #1-bis in August 2023, and case #1-tris in September 2023; See Table 2). All subjects were male aged from 24 to 64 years (median: 41 years; see Table 2). The estimated time elapsed from the last substance intake to the ED admission ranged from 1 to 72 h. In 12 cases, both blood and urine were collected. In 3 cases were available only blood samples and in 2 cases only urine. MDPHP concentrations ranged from 1.26 to 73.30 ng/mL (median: 12.79 ng/mL) for blood samples and from 19.31 to 8769.64 ng/mL (median: 635.62 ng/mL) for urine. Only case #4 showed a negative blood sample (urine: 608.81 ng/mL); the other cases had MDPHP positivity in both biological fluids. Besides MDPHP, α-PHP was detected in the blood of case #3 (46.44 ng/mL) and in the urine of case #1-tris (253.47 ng/mL) and case #2-bis (12.57 ng/mL). Urine analysis showed the concomitant use of cocaine in 14 cases, THC in 3 cases, and MDMA/amphetamines in one case.

We observed the exclusive use of MDPHP in only one case, by

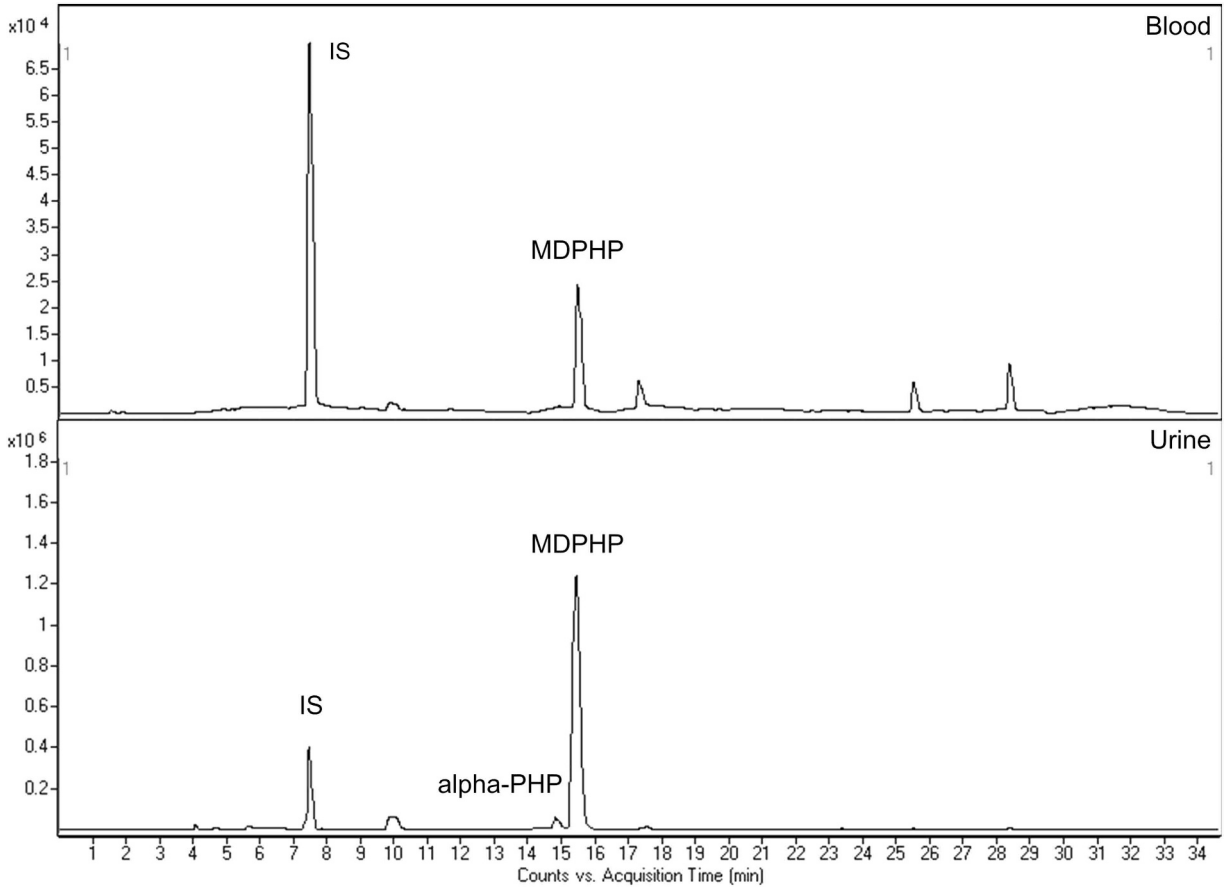

Fig. 2. Chromatogram for case #1-tris.

Table 2
Description and main findings of the cases included in this study.

Case	Age	MDPHP (ng/mL)		Other substances		BAC	Route of Intake	Frequency of Intake	Time since last Intake (in hours)	Substances Reported by the patient
		Blood	Urine	Urinary test	LC-MS/MS (ng/mL)					
#1	40	48.07	8769.61	Cocaine	NEG	NEG	N/A	repeated	24-48	MDPV, cocaine/crack, GHB
#1-bis		8.66	5288.58	Cocaine, THC	NEG	*NEG*	*inh*	*repeated*	*0-12*	*MDPV*
#1-tris		35.63	4869.76	Cocaine, THC	α-PHP: 253.47 (urine)	*NEG*	*inh*	*repeated*	*0-12*	*MDPV*
#2	28	1.26	172.05	MDMA, AMP	NEG	NEG	inh	repeated	0-12	unaware
#3	38	73.3	np*	Cocaine	α-PHP: 253.47 (blood)	N/A	N/A	N/A	12-24	unaware
#4	59	NEG	608.81	Cocaine	NEG	NEG	inh	occasional	0-12	cocaine/crack, other unspecified substances
#5	33	20.37	5542.01	Cocaine	NEG	NEG	iv	occasional	0-12	unaware
#5-bis		14.72	1219.81	Cocaine	α-PHP: 253.47 (urine)	*NEG*	*inh*	*occasional*	*0-12*	*MDPV*
#6	64	10.86	2370.91	Cocaine	NEG	N/A	inh	N/A	0-12	PV, cocaine/crack
#7	33	np*	19.31	Cocaine	NEG	N/A	inh	repeated	0-12	MDPV, cocaine/crack
#8	58	64.22	np*	Cocaine	NEG	NEG	N/A	occasional	0-12	cocaine/crack, other unspecified substances
#9	46	3.48	351.04	Cocaine	NEG	NEG	inh	repeated	0-12	MDPV, cocaine/crack
#10	44	35.49	np*	Cocaine	NEG	NEG	inh	repeated	0-12	MDPV
#11	42	3.64	662.44	Cocaine, THC	NEG	NEG	N/A	N/A	0-12	cocaine/crack, other unspecified substances
#12	42	3.24	391.38	THC	NEG	NEG	inh	repeated	>48	MDPV, cocaine/crack
#13	30	np*	34.73	NEG	NEG	NEG	inh	occasional	12-24	unaware
#14	24	1.57	31.84	Cocaine	NEG	NEG	inh	N/A	12-24	MDPV, mephedrone, GHB

Case	Psychiatric Symptoms	Restlessness/ Psychomotor Agitation	Neurological Symptoms	Respiratory Symptoms	Elevated CPK	Tachycardia	Elevated troponins	New onset hypertension	Therapy in ED	HIV Therapy	Chemsex
#1	yes	yes	no	yes	N/A	yes	no	no	bdz + SGA/propofol	no	yes
#1-bis	*yes*	*yes*	*no*	*no*	*N/A*	*no*	*no*	*yes*	*bdz*	*yes*	*yes*
#1-tris	*yes*	*yes*	*no*	*yes*	*N/A*	*yes*	*N/A*	*no*	*bdz*	*yes*	*yes*
#2	yes	yes	yes	yes	yes	yes	yes	no	bdz + SGA/propofol	no	yes
#3	N/A	yes	yes	N/A	N/A	N/A	yes	no	bdz	no	no
#4	yes	yes	yes	no	no	no	yes	no	bdz + SGA/propofol	yes	no
#5	yes	yes	no	no	yes	no	no	no	bdz + SGA/propofol	yes	no
#5-bis	*no*	*yes*	*yes*	*yes*	*N/A*	*yes*	*yes*	*yes*	*bdz*	*yes*	*no*
#6	yes	yes	no	yes	N/A	yes	no	yes	bdz + SGA/propofol	yes	yes
#7	yes	yes	yes	yes	yes	no	no	no	bdz + SGA/propofol	yes	yes
#8	yes	no	no	yes	N/A	yes	N/A	no	not administered	no	no
#9	no	yes	no	no	yes	no	no	no	bdz	PrEP	yes
#10	no	no	no	no	no	no	no	yes	bdz	no	yes
#11	no	no	no	no	N/A	no	N/A	no	not administered	yes	no
#12	no	no	no	no	yes	no	no	no	not administered	no	no
#13	no	no	no	yes	no	yes	no	no	not administered	no	no
#14	no	no	yes	no	no	no	no	no	bdz	no	yes

Table 1. Legend. Acronyms in alphabetical order:
α-PHP: α-pyrrolidinohexiophenone; AMP: amphetamines; bdz: benzodiazepines; ED: Emergency Department; BAC: blood alcohol content; inh: inhaled; iv: intravenous; LC-MS/MS: Liquid Chromatography-tandem mass spectrometry; MDMA: 3,4-Methyl enedioxy methamphetamine; MDPHP: 3,4-methylenedioxy-hexanophenone; N/A: not assessed or not available; np* : not provided; SGA: second generation antipsychotics; THC: Δ^9-tetrahydrocannabinol.
Italics, darker colour: multiple admission. Blue: chemsex. Pink: no chemsex.

inhalation (case 13). This patient was admitted to the hospital 18 h after MDPHP consumption. He reported the onset of chest pain one hour after the exposure to an unknown substance, which was followed by insomnia. No pathological findings were observed during clinical and instrumental evaluation. Inhalation (smoking) was the most common route of MDPHP exposure. The injection route was reported by a patient with a psychiatric disease history. He exhibited self-harm behaviour by jumping out of a moving vehicle on the way to the hospital, while under the substance influence. None of the patients intended to use MDPHP specifically thus consuming this molecule unawared. Patient's intention was to use either cocaine, other psychostimulant drugs or both. Ten patients expected to use other synthetic cathinones such as MDPV and PV. Polydrug abuse was observed in eight cases.

Almost all cases presented behavioural and neuropsychiatric symptoms, including anxiety, and psychomotor agitation, often accompanied by vivid alterations in sensory-perception domain (e.g., auditory and/or tactile hallucinations). Eight of them showed suspiciousness and persecutory delusions. One case reported a sense of depersonalisation. One patient showed a strong craving for MDPHP, which was probably related to both the frequent use and the short time elapsed since the last intake. Neurological symptoms such as stereotyped movements and dystonia of the neck and lower limbs were reported in four cases.

Other complications were observed in some cases. Five showed respiratory symptoms such as cough and dyspnoea and four of them had alterations on chest X-ray (for e.g., increased lung markings). Five showed various respiratory symptoms such as cough and dyspnoea; four of them had alterations on chest X-ray. Seven cases presented signs of potential cardiac toxicity, including new-onset hypertension, tachycardia, and increased troponin, with one case of P-wave inversion (ectopic focus-like) in the electrocardiogram (ECG). One case showed a transient mild increase in body temperature (38 °C). Eleven patients had mild alterations in their blood counts, while five patients had elevated creatine phosphokinase (CPK). No significant changes in methemoglobinemia or carboxyhemoglobinemia were observed in the arterial blood gas analysis.

In some cases, it was necessary to carry out more detailed laboratory and instrumental investigations, such as chest X-rays and computed tomography (CT) scans in order to assess the severity of the possible lung damage.

Eight cases out of fourteen had no previous psychiatric diagnosis while nine patients had a previous SUD. Six patients were already being treated with psychotropic medication and seven were on antiretroviral therapy for HIV (one was routinely taking PrEP-Pre-Exposure Prophylaxis). Finally, eight cases reported to use psychostimulants in the context of chemsex sessions. See Table 2 and Supplementary Materials for further details.

3.2. Treatment administered and clinical outcomes

Symptomatic treatment was required in all cases. One patient refused the proposed therapies. Treatments included intravenous hydration, benzodiazepines and, in some cases, antipsychotics. Oxygen therapy was also required in some patients. Most patients had a rapid improvement in their acute symptoms and were discharged after a short period of observation in the emergency department. Only one patient with a pre-existing psychiatric disorder had to be transferred to an inpatient psychiatric unit. The length of stay in the ED was 1.56 ± 0.6 days for patients who did not require further medical observation.

4. Discussion

To date, this is the largest case series describing the toxic effects of MDPHP in Italy. Our work also illustrates the treatments applied to manage acute MDPHP intoxication in a hospital setting.

In line with recent European reports, we observed an increase in the number of cases identified in 2023 compared to the data collected in 2022 [7].

The short- and long-term effects of SCs are poorly understood, including the potential acute neurological effects [22–25]. Their actual health consequences are only partially characterised due to fragmentary clinical documentation, incomplete knowledge of the phenomenon, and limited biological samples for toxicological analysis [22,26–29].

Our main findings were related to psychiatric, respiratory, and cardiac manifestations. The observed clinical effects are consistent with previous findings related to exposure to other SCs. In fact, in our case series, the most commonly reported symptoms were related to sympathomimetic effects, with an increased incidence of aggressive behaviour, hallucinations, and paranoia, as previously observed [30,31].

Consistent with previous findings, SCs (e.g., MDPV) and other NPS, could impair mental state and cause psychotic manifestations, both alone and in combination with other drugs of [32–35]. Some Authors highlighted a wide range of other psychotropic effects (e.g., psychomotor agitation, aggressiveness, delusional ideation), which were observed in our case collection [36,37]. In particular, several studies demonstrated that MDPV enhances aggressiveness with greater potency and efficacy than cocaine, especially in case of repeated administration; moreover, aggressive behaviours may also be enhanced by co-consumption of ethanol [38,39].

Despite the short half-life of the drug, clinical manifestations appeared to persist for 12–24 h, then tended to resolve rapidly. More prolonged effects were associated with respiratory symptoms and psychiatric issues, with typical persistence of paranoia-related problems and behaviours.

Although some patients reported repeated use of psychostimulants, we did not observe withdrawal syndrome in contrast with both literature and anecdotal reports for SC class [40].

Alterations in respiratory patterns are unlikely to be due to a specific effect of the substance itself. Rather, they appear to be related to the route of administration. Indeed, patients with acute respiratory symptoms had inhaled the substance, and those with alteration in chest X-rays reported repeated use of smoking drugs.

Patients with increased CPK (ranging from 593 to 4640 U/L at the ED admission) did not manifest renal failure. This may be related to adequate hydration administered in the ED, highlighting the importance of supportive therapy. The observed blood count alterations can be attributed to various causes/comorbidities, e.g., dehydration, spleen contraction (both due to neural input and catecholamine release), and HIV positivity.

Previous findings showed that the consumption of SCs can trigger various psychiatric symptoms such as agitation, anxiety, paranoia, hallucinations, and delusions. as well as increased risk of suicide attempts and a greater occurrence of mood, anxiety, and psychotic disorders [41,42]. Indeed, our case series showed similar pathological associations. For instance, a psychiatric patient with a history of repeated NPS use jumped from a moving car and injured himself after an intravenous injection of MDPHP, and then manifested signs of agitation and psychosis in the ED.

Another psychiatric patient with a diagnosed cluster B personality disorder and a history of chemsex and HIV presented to the emergency department on two separate occasions, after repeated SC use, with similar acute psychopathological disturbances. The latter patient also highlighted the risk of frequent multiple hospital admissions in patients with substance-induced psychosis [43]. Neurotoxicity in dopaminergic and serotonergic neurons, which play a critical role in regulating mood and mental health, is likely a contributing factor for the development of psychiatric symptoms in SCs users [11].

Unfortunately, we identified only one case that was exclusively positive for MDPHP. Therefore, it is difficult to attribute the symptomatology to MDPHP alone in all other cases. However, as with other substances, it is noteworthy that physical symptoms, anxiety, psychomotor agitation, and craving were more pronounced a few hours after exposure. The paranoid symptoms seemed to persist even after a longer

period from the last reported use of the substance. However, it should be considered that chemsex sessions may last several days and that some patients may not only have been exposed to repeated doses and multiple substances but may also be predisposed to psychiatric conditions.

In line with the literature we found only male cases Indeed, NPS poly-addicts were typically young males with a history of multiple ED admissions [34,44–49]. Sex and gender differences in the use of MDPHP and NPS in general need to be further investigated and understood [50].

Fortunately, none of the reported cases resulted in a fatal outcome. However, this risk should be considered especially in the case of repeated use (in a single session or on several occasions), delayed access to the ED, or the tendency of some patients to minimise health-related risks. It should also be noted that the only MDPHP fatality reported in the literature showed 222 ng/mL and 399 ng/mL of the substance in the urinary and blood samples, respectively.

The observed symptoms may however have been enhanced or related to synergism with other substances of abuse or drug therapies taken. Overall, therefore, poly-drug use and in particular the co-administration of cocaine, which is potentially responsible for at least partly overlapping symptoms, must be considered.

The described effects appear to be correlated with the MDPHP intake, but it is difficult to establish a specific correlation. This may be due to several reasons: 1) initial dose 2) time elapsed since intake 3) possible active effects of metabolites 4) psychiatric comorbidity 5) individual propensity to manifest predominantly motor or psychiatric symptoms.

In our opinion, the management of this type of intoxication should be directed toward supportive and symptomatic treatment. No specific antidotes are currently available. Decontamination also plays a marginal role, even considering the main exposure route.

In acute cases, the following treatments appeared to be effective: A) Adequate hydration. This has been useful both in patients who presented to the ED dehydrated for various reasons, to treat potential rhabdomyolysis, and to prevent the risk of renal failure. B) Benzodiazepines (e.g., diazepam or lorazepam), given their favourable pharmacokinetic profile, if appropriately dosed, according to the nature and duration of the symptoms. Benzodiazepines may also offer a protective effect in the case of possible hyperpyrexia and convulsions, as observed in previous SCs' reports and in cases of ambiguous intakes. C) Antipsychotics for acute psychotic manifestations that have not been adequately treated with benzodiazepines.

As noted by some Authors, the management of psychomotor agitation is a primary goal; as well, some patients may only need reassurance, support, and medical monitoring [23,51]. Therefore, we emphasize the importance of alleviating cravings and any psychotic symptoms.

On the basis of the clinical/laboratory findings and the patient's medical history, we also emphasise the importance of carrying out infectious disease, cardiological and psychiatric consultations, as well as not underestimating the importance of instrumental diagnostics, especially ECG, chest X-ray, CT scan, and electroencephalogram (EEG).

5. Limitations

Our study has several limitations. First, the number of cases. Although we collected all cases that presented to the EDs during the observed period, some factors may likely discourage users from accessing the ED (e.g., shame, fear of legal consequences, stigma for psychiatric manifestations, and poor perception of the seriousness of the potential consequences of drug use). A larger sample would be useful to analyse other possible facets and enrich the range of possible clinical manifestations.

A randomized clinical trial could be useful to define the most effective aspects of treatment in the acute setting and the most appropriate kind of counselling to perform, even in contexts of limited healthcare resources. We tried to standardise data collection. However, we encountered slight differences in reporting procedures among the various healthcare professionals in EDs, making this process challenging. In our study, the possible long-term consequences of using MDPHP, including addiction potential, the occurrence of withdrawal symptoms, and psychotic exacerbations, were not investigated in detail. There are also concerns regarding the occurrence of related mild/transient neurological disturbances. Further investigation is warranted to explore the sexual habits of people using this type of substance and their patterns of use. Finally, another potential limitation is the correlation between symptoms and detected concentrations, which may be influenced both by the time between consumption and sampling and by treatments received (e.g., hydration and other intravenous interventions that may affect observed concentrations).

6. Conclusions

SCs, including MDPHP, are potential causes for admission to ED. Emergency physicians should be prepared to consider MDPHP assumption in case of intoxication when symptoms can not be explained by the intake of common drugs of abuse. Further, the healthcare personnel should require further analysis to investigate the presence of NPS. MDPHP causes dystonia, psychomotor agitation, delirium, and sensory-perception alterations. Attention must be paid in case of airway irritation/respiratory failure and altered ECG tracings. The effects of co-administration with other drugs of abuse may be unpredictable. Intensive supportive approaches may be required. Moreover, this study underlined again that routine screening tests are unable to detect these substances. Thus, the adoption of validated analytical methods for the detection of a high number of NPS is important for forensic toxicology laboratories. Further studies are needed to delineate patterns of use and associated symptoms. Preclinical studies could elucidate the exact mechanisms of action, as well as the eventual addiction potential. We also recommend the implementation of homogeneous data collection strategies in the various treatment centers, to facilitate the processes of analysis, differential diagnosis, and information submission to the institutions involved in monitoring the substance's toxic effects. Along with greater attention by emergency physicians, it might be useful to train other potentially involved disciplines consultants (medical toxicologists, psychiatrists). Finally, it is essential to warn possible users, both among young people and in addiction treatment centers.

Author statement

All the authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. The authors confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. The authors further confirm that the order of authors listed in the manuscript has been approved by all of us.

CRediT authorship contribution statement

Dimitrova Alexandra: Investigation. **Totti Arianna:** Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Di Milia Maria Grazia:** Resources, Investigation. **Croce Emma Beatrice:** Investigation. **Gualco Barbara:** Writing – original draft. **Gambassi Francesco:** Supervision, Resources. **Pieraccini Giuseppe:** Investigation. **Vaiano Fabio:** Writing – original draft, Visualization, Validation, Project administration, Investigation, Data curation, Conceptualization. **Mannaioni Guido:** Writing – original draft, Visualization, Supervision, Resources. **Arillotta Davide:** Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpba.2024.115974.

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