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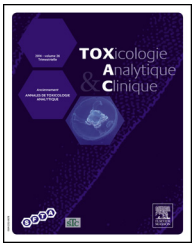

CASE REPORT

Case series of severe intoxications associated with new psychoactive substances on Reunion Island: Clinical description and diagnostic challenges

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Summary
Background. — New psychoactive drugs appeared in Reunion Island beginning in 2016, principally synthetic cannabinoids such as ''tabac chimique''. We described the clinical features of twelve hospitalizations during 2023—2024 requiring admission to intensive care unit for suspected psychoactive drug intoxication with atypical clinical presentation for synthetic cannabinoids, including a morphine-like toxidrome.
Results. — Over a ten-month period, twelve patients aged from 21 to 43 years required treatment in the intensive care unit with a suspected psychoactive drug intoxication. The main cause of intensive care unit admission was a profound coma with early acute respiratory failure. All patients except one developed acute respiratory distress syndrome, with six being severe and ten requiring intubation with mechanical ventilation. Four patients experienced hemodynamic shock. Five exhibited acute heart failure, with three requiring inotropic drugs. Five patients

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developed acute renal failure and one patient developed acute liver failure. Most of the patients confirmed inhaling ''tabac chimique''. Two blood and urine samples were positive for the novel synthetic opioid Protonitazene, one was associated with a novel synthetic cannabinoid. Another analysis was positive for a metamphetamine analogue.
Conclusions. — Inhalation of new psychoactive substances including novel synthetic opioids can lead to severe organ failure with a life-threatening prognosis, with neurological and respiratory failure initially, followed by early acute cardiac failure.

Abbreviations

NSC	new synthetic cannabinoids
NPS	new psychoactive substances
ICU	intensive care unit
RHA	regional health agency
ARDS	acute respiratory distress syndrome
AKI	acute kidney injury
NSO	new synthetic opioids
GSC	Glasgow coma scale
LVEF	left ventricular ejection fraction
VTI	velocity time integral
ECG	electrocardiogram
MOR	mu-opioid receptor
NCPE	non-cardiogenic pulmonary edema

Background

Reunion Island is a French department in the Indian Ocean with a population of 870,000 inhabitants. It has cultural links with the French overseas department of Mayotte. On Reunion, the extent of cannabis abuse is the highest in France and there is a high consumption of diverted psychotropic drugs, including Trihexyphenidyle chlorydrate and Clonazepam. In recent years, there has been an increase in the abuse of ecstasy and cocaine [1].

From the early 2010s, a new phenomenon emerged in Mayotte called ''chimique'' or ''tabac chamanique'', involving smoking a mixture of tobacco soaked in alcohol and novel synthetic cannabinoids (NSC) [1]. Since 2016, due to close links between the two islands, ''chimique'' consumption has spread to Reunion, most often consumed in the form of powder, diluted in solvent, sprayed on tobacco. There has simultaneously been an increase in customs and police seizures of New Psychoactive Substances (NPS) [1,2]. The experimentation rate appears to be high, particularly with young people in social and financial insecurity, with use also reported in prisons [2].

In 2023 and 2024, we witnessed several cases of serious intoxication resulting in hospitalization in our intensive care unit (ICU). Most of the patients admitted having taken ''chimique'' but did not exhibit the usual signs of NSC poisoning such as delirium, seizures and agitation. Their clinical presentation more closely resembled opioid syndrome, and their clinical condition was, in some cases, extremely serious. Consequently, we reported the incidents to the Regional Health Agency (RHA), which subsequently initiated monitoring measures as well as prevention plans with healthcare professionals and the general public [3]. The entirety of these cases is summarized in this study.

Method

This is a retrospective case series of all patients with suspected NPS intoxication admitted to the ICU of the University Hospital of Reunion between May 2023 and March 2024. The aim of the study is to describe a series of intoxications linked to the presumed use of NPS that led to hospitalization in ICU. Biological matrices collected less than 24 hours after suspected consumption of NPS were preserved at −20 °C. Samples were shipped by airfreight to the laboratory of Bordeaux University Hospital accompanied by a detailed data sheet. The blood and urine samples underwent liquid-liquid extraction using both alkaline and acidic methods, follow by non-targeted analysis using gas chromatography—mass spectrometry (GC-MS) and ultraperformance liquid chromatography—high resolution mass spectrometry (UPLC-HRMS). The mass spectra of unknown compounds detected in the biological samples were compared with those of a library to identify potential matches. The data was analyzed using the Cayman Spectral Library and SWG Drug databases for GC-MS, and Waters and HighResNPS databases for UPLC-HRMS, which collectively contain over 4,000 compounds including medications, narcotics, designer drugs and metabolites.

Data collection and analysis

Medical records were retrospectively reviewed to identify demographic data, clinical characteristics, intoxication details, organ failure during ICU stay and their management, and length of stay in ICU and hospital. Information on the drug and their methods of consumption were also collected when the patient woke up in ICU, or later in hospital or

in an addictological consultation. Toxicologic analysis was reviewed retrospectively.

Results

Case cluster

In the ICU of the University Hospital of Reunion, there were 12 hospitalizations for suspected NPS intoxication between May 2023 and January 2024 (eight males, including one hospitalized three times and another hospitalized twice, and one female, all aged 21 to 43), with an unusual clinical presentation for NSC use (Table 1). Three of the nine patients were incarcerated at the time of the initial care. The reason for admission to ICU was coma for ten of the twelve hospitalizations, and acute respiratory distress and cardiac arrest for the other two patients. They were all calm comas, with bradypnea in over 50% of cases and miosis in at least six cases (pupil status was not always collected), suggesting opioid toxidrome.

Upon admission to ICU patients were in critical condition with a median SOFA score of 11 (predictive of a 40% to 50% mortality rate). Four patients experienced hemodynamic shock, three of which had a cardiogenic component, with acute cardiac failure regressing within 24 hours. All patients but one (first hospitalization of case 8) presented with acute respiratory distress syndrom (ARDS), including six severe cases. ARDS diagnosis was made using the 2024 definition and 2012 Berlin criteria [4,5]. Regarding patients suffering from cardiotoxicity related to the consumed molecule, the pulmonary radiological abnormalities were not explained by volemic overload. All patients but one were intubated and mechanically ventilated, and one patient was treated with high-flow nasal oxygen therapy. ARDS management was based on the 2019 guidelines, with a curarisation in case of a persistent PaO2/FiO2 ratio < 150, Cisatracurium being the molecule used in this case series. Four patients had hemorrhagic secretions, one of whom had a CT scan suggesting intra-alveolar hemorrhage. Six patients developed acute kidney injury (AKI), and one patient had hepatic cell failure.

Toxicological urine analysis found the presence of cannabis in five cases, tricyclic antidepressants in two cases, and ecstasy in one case. In eight cases, ''chimique'' consumption was subsequently confirmed by the patient, with the product being smoked; patients were expecting to consume NSC and were not aware of the presence of new synthetic opioids (NSO) in the product.

Toxicologic analysis for NPS was not performed in three cases, returned negative in six cases, and was positive in both blood and urine in three other cases. One analysis identified Protonitazene, one found an association of Protonitazene and an NSC, and one a metamphetamine analogue. The median length of stay in ICU was six days.

Case 1

A 32-year-old man, incarcerated at the time, was hospitalized three times in our ICU over a four- month period for coma. The Glasgow Coma Scale (GCS) scores at admission were 9, 4, and 3 respectively, and accompanied with bradypnea and breathing pauses. On the third hospitalization, a bipallidal hypodensity was detected on the contrast-enhanced brain CT scan. The patient required short-term mechanical ventilation on each hospitalization, and received antibiotic treatment for aspiration pneumonia on two occasions. He required only low doses of vasopressors and did not exhibit cardiac failure. Urine toxicology analysis revealed the presence of cannabis, benzodiazepines and tricyclic antidepressants on the first admission. Blood tests for NPS returned negative, but the patient later confirmed having smoked ''chimique''.

Case 2

A 29-year-old woman was hospitalized for respiratory distress and altered consciousness. Following a week of digestive issues and flu-like symptoms at home, the patient was found drowsy, with stertoreous breathing, drooling and loss of bladder control. When she regained consciousness, she presented with chest pain, dyspnea and abundant hemoptysis. On ICU admission, her GCS was 14, with tachycardia, signs of extracellular dehydration, diffuse abdominal pain and psychomotor agitation, but no fever. She presented with respiratory distress progressing to moderate ARDS requiring high-flow nasal oxygen therapy. Biological analyses showed an inflammatory syndrome and an increase of D-Dimers at 15,000 µg/L and a troponin blood concentration of 178 ng/L. A thoracic CT scan eliminated a pulmonary embolism and revealed bilateral micronodules which could be indicative of intra-alveolar hemorrhage. The patient did not require vasopressors but experienced cardiac failure with a global decrease in left ventricular ejection fraction (LVEF) on echocardiography, a moderate right ventricle failure and diffuse ST-segment elevation on electrocardiogram (ECG). A first-line etiological assessment for myocarditis returned negative (serologies for the main viruses involved, search for major autoimmune diseases and for bacterial infection), but no cardiac imaging, coronary angiography or myocardial biopsy was performed because of rapid improvement and high imputability related to intoxication. Urine toxicology screening for NPS found the presence of N-methyl-2-aminoindane, a psychoactive drug, analogue of methamphetamine. The patient confirmed having smoked ''chimique''.

Case 3

A 21-year-old man, incarcerated at the time, was admitted for non-shockable cardiorespiratory arrest with fifteen minutes of low flow and return of cardiac activity after 1 mg of epinephrine. The patient then presented with respiratory failure under mechanical ventilation with a 62% SpO2 in FiO2 100%. Early progression led to cardio-circulatory failure. Cardiac sonography showed a collapsed LVEF without right ventricular dysfunction. The patient required high doses of norepinephrine and dobutamine. He was mechanically ventilated for seven days, suffered from severe ARDS and required curarisation. Urine and blood toxicology screening found traces of cannabis and benzodiazepines, but returned negative for NPS. The patient confirmed having consumed ''chimique''. He was readmitted to ICU twenty-four hours after initial discharge due to respiratory distress caused by

Table 1 Data of 12 cases of suspected NPS intoxication in the ICU of University Hospital of Reunion (Saint Denis), 2022—2024.

	Case 1			Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8		Case 9
	Hospit 1	Hospit 2	Hospit 3	Hospit 1	Hospit 1	Hospit 1	Hospit 1	Hospit 1	Hospit 1	Hospit 1	Hospit 2	Hospit 1
Age	32	29	21	27	31	22	43	32	25			
Sex	M	F	M	M	M	M	M	M	M			
SOFA score	5	11	10	3	13	14	13	13	11	1	10	13
Initial Glasgow score	9	3	4	14	3[b]	3	3	3	3	3	3	3
Bradypnea at first care	Yes	Yes	Yes	No	NA	Yes	Yes	Yes	No	Yes	Yes	Yes
Miosis	NS	NS	NS	No	NS	Yes	Yes	Yes	No	Yes	Yes	Yes
Naloxone	No	No	No	No	No	0,12 mg: useless	0,4 mg: usefull	No	No	0,48: usefull	No	No
Minimal P/F ratio[a]	219	172	233	205	48	43	53	64	86	NA	200	55
Length of mechanical ventilation (days)	1	2	2	0	7	3	5	7	5	1	3	5
Aspiration pneumonia	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Maximum norepinephrine dose	0	low dose	low dose	0	2,1 μg/kg/min	3,8 μg/kg/min	Low dose	0,4 μg/kg/min	Low dose	Low dose	Low dose	0,26 μg/kg/min
Acute cardiac failure	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	Yes
Maximum dobutamine dose	0	0	0	0	8 μg/kg/min	2 μg/kg/min	0	5 μg/kg/min	0	0	0	0
Renal failure	No	KDIGO1	No	No	KDIGO 1	KDIGO 3	KDIGO 1	KDIGO 2	No	No	No	KDIGO 1
Positive NPS test	No	No	No	Met analogue[c]	No	Protonitazene	Protonitazene+ Synthetic cannabinoid (MDMB-4en-PINACA)	No	No	No	No	No
Route of administration	Inhaled	Inhaled	Inhaled	Inhaled	Inhaled	Inhaled	Inhaled	Inhaled	Unknown	Inhaled	Unknown	Unknown
ICU stay (days)	2	3	3	3	8	6	6	9	6	1	3	6

Hospit: ICU hospitalization; NS: not specified; NA: not applicable.
[a] Minimal P/F ratio: lowest PaO2/FiO2 ratio during hospitalization.
[b] Cardiac arrest.
[c] Metamphetamine analogue: N-methyl-2-aminoindane.

a bilateral pulmonary embolism. Evolution was good under simple oxygen therapy and anticoagulation.

Case 4

A 27-year-old man was admitted to ICU for coma with a GCS of 3 with bradypnea, bradycardia, bilateral miosis and hypothermia at 29 °C; 0.12 mg of intravenous naloxone did not improve neurological status. The initial brain CT scan showed bilateral hippocampal edema. The patient exhibited hemodynamic instability with a severe cardiac dysfunction on echocardiography. ECG revealed Osborn J waves and troponin blood concentration was increased to 406 ng/L. The patient required inotropic support with dobutamine and high doses of norepinephrine. Additionally, he exhibited KDIGO 3 renal failure and hepatic insufficiency with hypoglycemia. Hepatic cytolysis reached ASAT levels of 835 IU/L and ALAT levels of 538 IU/L with a minimum prothrombin level of 49%, and Factor V at 16%. The patient was intubated for three days, with severe ARDS requiring curarisation, nitric oxide, and several sessions of prone positioning. Urine toxicology screening only detected benzodiazepines, and NPS screening returned positive for Protonitazene in both blood and urine. The patient later confirmed having smoked ''chimique''.

Case 5

A 31-year-old patient was admitted to ICU for coma with a GCS of 3 after head trauma in a context of drug inhalation associated with bradypnea, bilateral miosis, hypothermia (34 °C) and sweating. A friend of the patient also presented with impaired consciousness. Intravenous administration of 0.4 mg of Naloxone improved ventilatory status, with normalization of respiratory rate, but an oro-tracheal intubation was performed due to persistent coma. A brain CT scan showed no abnormalities. The patient developed moderate cardiac failure with an altered LVEF and required low doses of vasopressors. Ventilatory status evolved to severe ARDS necessitating curarisation. Urine toxicology screening revealed the presence of cannabis and benzodiazepines, while NPS tests detected Protonitazene and MDMB-4en-PINACA (an NSC) in both blood and urine. The patient later confirmed having smoked ''chimique'' but was unaware that he was consuming an opioid at the time.

The patient's friend was admitted to the emergency department for a less severe neurological condition. He reported having consumed the same substance, but in lesser quantities. NPS screening found a synthetic cannabinoid but no synthetic opioids.

Case 6

A 22-year-old, recently incarcerated patient was admitted to ICU for coma with a GCS of 3, bradypnea and bilateral miosis. He presented with severe ARDS requiring curarisation. Upon admission, cardiac function was satisfactory but rapidly evolved within the first hours to severe heart failure. ECG showed an ST-segment depression in lateral territory and troponin blood concentration was increased to 1845 ng/L. He required vasopressors and inotropic support by Dobutamine. Urine toxicology revealed presence of cannabis, benzodiazepines and tricyclic antidepressants, while NPS tests returned negative. The patient confirmed taking ''chimique''.

Case 7

A 43-year-old man, incarcerated at the time, with a history of tobacco, cannabis, and alcohol consumption, was admitted to ICU for coma with a GCS of 3, bradypnea and elevated blood pressure, suspected aspiration and intermediate and reactive pupils. Brain CT scan and ECG showed no abnormalities while cardiac sonography revealed a moderate left ventricular dysfunction. He presented with severe ARDS with quick improvement. NPS tests returned negative.

Case 8

A 32-year-old man with a history of alcohol, tobacco and cannabis use, was hospitalized twice in ICU. He first presented with a coma of GCS 3, bradypnea, bilateral miosis, sweating, and acute respiratory failure. Initial intravenous administration of 0.24 mg naloxone did not improve clinical status, but an additional dose of 0.24 mg improved respiratory and neurological condition to a GCS of 15. The chest CT scan showed abnormalities consistent with an infectious involvement and brain CT scans revealed no abnormalities. Biological exams showed a mixed acidosis and hyperkalemia at 7.8 mmol/L with a type 1 atrio-ventricular block in the ECG. He was treated with insulin, glucose and antibiotics due to suspected aspiration pneumonia. The patient displayed anxiety and left the hospital against medical advice the same evening. He denied having used drugs, and claimed to have only smoked a cigarette prior to hospitalization. No toxicological analysis could be performed.

During his second hospitalization in ICU six months later, the patient presented once more with coma at GCS 3, bradypnea, bilateral miosis and respiratory failure, without obvious head trauma or seizure. He presented aspiration during intubation. ''Chimique'' was found in the patient's personal effects. In ICU he presented with moderate ARDS. Toxicology screening returned negative and the patient self-discharged again, against medical advice, after a three days ICU stay.

Case 9

A 25-year-old man with a history of tobacco and cannabis use was found in the street unconscious with a GCS of 3, bilateral miosis and bradypnea, hypothermia at 32 °C and presenting acute respiratory failure with SpO2 20% in ambient air requiring immediate intubation. CT scans showed no brain abnormalities and extensive bilateral infectious lung disease. He presented with severe ARDS requiring curarisation, hemodynamic instability with an altered LVEF and global cardiac hypokinesia, a diffuse sus-ST on ECG and a troponin blood concentration of 59 ng/L. Hemodynamic and respiratory failure rapidly improved with antibiotic therapy. Toxicology screening was negative.

Discussion

Between May 2023 and March 2024, twelve cases of suspected NPS poisoning were admitted to the ICU of the University Hospital of Reunion (Saint Denis), three of which were confirmed. Clinical presentation was unusual owing to the initial severity of symptoms, with an average SOFA score of 11 predicting a mortality of almost 50%.

Organ failure was primarily neurologic and pulmonary, and some patients rapidly presented severe cardiac dysfunction. Evolution was favorable for all patients, with a clear improvement in clinical condition after the first 24 hours of symptomatic treatment.

Most patients presented with an opioid syndrome with calm coma, bradypnea and miosis. Two toxicologic analyses returned positive for protonitazene, a drug which was seized in a prison a few weeks before the first cases occurred. Protonitazene seems to be widely circulating in the prison setting of Indian Ocean's French departments, since along with our ICU hospitalizations, four deaths due to protonitazene's intoxication in prison were confirmed: two on Mayotte and two on Reunion island [6,7]. Protonitazene is a synthetic benzimidazole synthesized in the 1950s as an alternative to morphine, and was abandoned due to high levels of adverse effects. It was first reported in forensic sampling in 2019 in North America and is a public health issue in countries such as Canada and the USA, where Fentanyl and new synthetic opioids (NSO) other than methadone are responsible for 70% of the 107,941 drug overdose deaths in 2022 [8,9].

Cardiovascular events are known to be linked to opioid overdose, particularly myocardial infarction and arrhythmia, even though it is not specific and may be related to other NPS intoxications [10]. Classical signs are bradycardia and low blood pressure for natural opioids (due to the MOR-mediated vasodilatation) and arrhythmia linked to ion-transporter blockade for synthetic opioids [11]. Acute heart failure is less common and seen in less than 1% of opioid overdose hospitalizations. The mechanism is not clear in the absence of myocardial infarction and arrhythmia [10,12].

Non-cardiogenic pulmonary edema (NCPE) is a typical complication of opioid (mainly heroin and methadone) overdose, with a complex pathophysiology, including an increase in pulmonary histamine released by heroin causing an increase in pulmonary capillary permeability [13,14]. In our cluster, ARDS could be a direct effect of the molecule on the lungs, but is more likely to be multifactorial, with infectious and chemical participation linked to frequent aspiration, associated with a cardiogenic pulmonary edema for patients presenting with heart failure. Naloxone-induced pulmonary edema has also been described, even at low doses [15]. In a case series of 27 patients with heroin-related NCPE, most respiratory failures were resolved within 24 hours, and only a third of the patients required mechanical ventilation for one day, contrasting with our cluster where 83% of patients needed intubation with a median mechanical ventilation time of three days [14].

Fifty percent of the patients in our series presented with AKI, especially those with hemodynamic instability. In opioid overdose, the mechanism behind AKI is often multifactorial, caused by dehydration, hypotension, rhabdomyolysis and urinary retention. Alterations in autonomic nervous and renin-angiotensin-aldosterone systems can also decrease cardiac output and renal blood flow leading to renal ischemia [16]. It is well established, particularly in septic shock studies, that despite a normalization of serum creatinine there is an increased risk of chronic kidney disease and long-term all-cause mortality, probably explained by a reduced number of nephrons, vascular insufficiency and maladaptive repair mechanisms [17,18].

Even though NSO poisonings leading to admission to ICU is common, mainly due to coma or cardiac and respiratory arrest, the presentation of our cases was quite unusual with rapid progression to critical ARDS, hemodynamic instability and cardiac failure. Evolution for all patients was favorable, with apparent total recovery from organ failure.

However, subjects who present with a non-lethal opioid overdose have an increased mortality risk with a 5.5% likelihood of death after one year, with 20% of these deaths occurring in the month following the overdose [19]. In addition, neurons are particularly vulnerable to hypoxia caused by opioid-induced respiratory depression, which was aggravated in our cluster by the frequency and severity of ARDS. Our patients did not benefit from a neuro-cognitive evaluation on discharge from hospital or later.

Neurological damage of varying severity can occur following opioid overdose, ranging from memory and attention disorders to epilepsy and motor deficits [20]. Furthermore, in our cluster, brain CT scans revealed abnormalities such as bi-pallidal hypodensity or bilateral hippocampal edema that can indicate neurological suffering. We also cannot eliminate the presence of chronic pulmonary and cardiac sequelae.

Despite a strong clinical suspicion of NSO poisoning in our cluster, most tests for NPS returned negative even though all samples were taken within hours of poisoning. The identification of highly potent products like NSO is challenging in broad-spectrum toxicological analysis, as even very low concentrations can produce a significant effect [21]. Human concentrations reported in the literature range from 1 to 10 ng/mL, well below the toxic concentrations of morphine, which generally start at around 100 ng/mL [22—24]. By way of comparison, in deceased patients from the same geographical area who had consumed protonitazene, probably by the same route, four out of five cases showed femoral blood concentrations of 0.1 ng/mL or less, with the fifth case at 0.8 ng/mL, and urinary concentrations ranged from 0.4 ng/mL to 2.9 ng/mL [7]. It is likely that our non-targeted analytical processor identifying NPS is less sensitive than this specific method for quantifying protonitazene. On the other hand, the concentrations in our living patients may be much lower, which could be attributed to various toxicokinetic parameters. Case 5 of our cluster highlights the issue of dose: for the patient who consumed a larger quantity, NPS screening was positive for both protonitazene and NSC, while for the patient who consumed a smaller amount, only NSC was detected. There is also the time between consumption and sampling, which is often unknown [25]. Studies on rodents show that NSO has a short detection window, as it is quickly metabolized and eliminated from the body [26]. The combination of these factors could explain why protonitazene is not found in all our living cases. In the USA, a recent prospective study of 537 patients with suspected acute opioid overdose in the emergency department and

laboratory testing for NPOs, found that only 2% of patients were positive for only fentanyl and 1.7% for NPOs (Brorphine, Isotonitazene, Metonitazene, or N-piperidinyl etonitazene), highlighting the difficulty in detecting these substances [27]. Access to other matrices and the use of a targeted method may be necessary to confirm overdose suspicions when blood and urine samples are negative. This could include hair analysis, although this technique may not be sensitive enough to detect a single exposure to protonitazene, or bile analysis, where concentrations can be up to 7 times higher than in blood [6,7].

Since March 2024, no further cases have been reported in Reunion. This corresponds to the conventional lifespan of NSOs in the literature, which is 6 to 12 months [28]. Most drugs circulating on the black market are never identified as they are quickly replaced by new substances as soon as a drug is brought under legislation. In our insular context, it is more likely that the rapid disappearance of this product owes to the fact that it is not sought after by drugs users; levels of opioid and heroin consumption is very low [2]. All patients in our cluster believed they were consuming NSC by smoking ''tabac chimique''. The presence of NSO in these products triggered fear and distrust in its consumers. Furthermore, prompt reporting of these poisonings ensured a rapid and effective response by the authorities, and the dismantling of the network.

For some patients in our cluster, administration of naloxone resulted in clinical improvement, particularly repeated doses. Naloxone is a high-affinity competitive opioid receptor antagonist very effective in natural or semi-synthetic opioid intoxication such as heroin. Its effectiveness is uncertain for overdoses of synthetic opioids such as Fentanyl or Benzimidazoles. The Health Advisory Network stipulates that multiple doses of naloxone may be necessary in cases of overdose with Fentanyl and similar drugs, including prolonged doses over time [29,30]. The lipophilicity of NSOs is over a thousand times that of morphine, allowing very rapid penetration into the central nervous system and other lipid-rich tissues, resulting in a rapid decrease in plasma concentration. This limits naloxone's effectiveness and exposes the patient to the risk of re-narcotization [31,32]. The answer may be found in the development of alternatives to naloxone with the development of a MOR-antagonist with higher affinity, faster absorption and prolonged action.

Conclusion

A drug name can encompass a wide range of products, which should lead to the greatest caution by both health professionals and consumers. NPS, and particularly NSO such as protonitazene, can cause severe health issues leading to ICU hospitalization, not only resulting in classic opioid overdose syndrome, but also the development of ARDS and acute heart failure.

Ethics approval and consent to participate

The study protocol was approved by the CNIL in February 2022, No. 921274 and by an institutional review board. Patient non-opposition was obtained with an information leaflet.

Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author on request.

Consent for publication:

Not applicable.

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Author's contributions

Research idea and study design: NN and BP; data acquisition: NN; data analysis and interpretation: NN, AM, BP; supervision and/or mentorship: AM, BP and DM.

Biochemical and toxicologic analysis: JG, AD, SB. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the whole work by ensuring that issues pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. NN and BP take responsibility for ensuring that this study has been reported honestly, accurately, and transparently and that no important aspects have been omitted. All authors have read and approved the final manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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