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New psychoactive substance cocktail in an intensive care intoxication case elucidated by molecular networking

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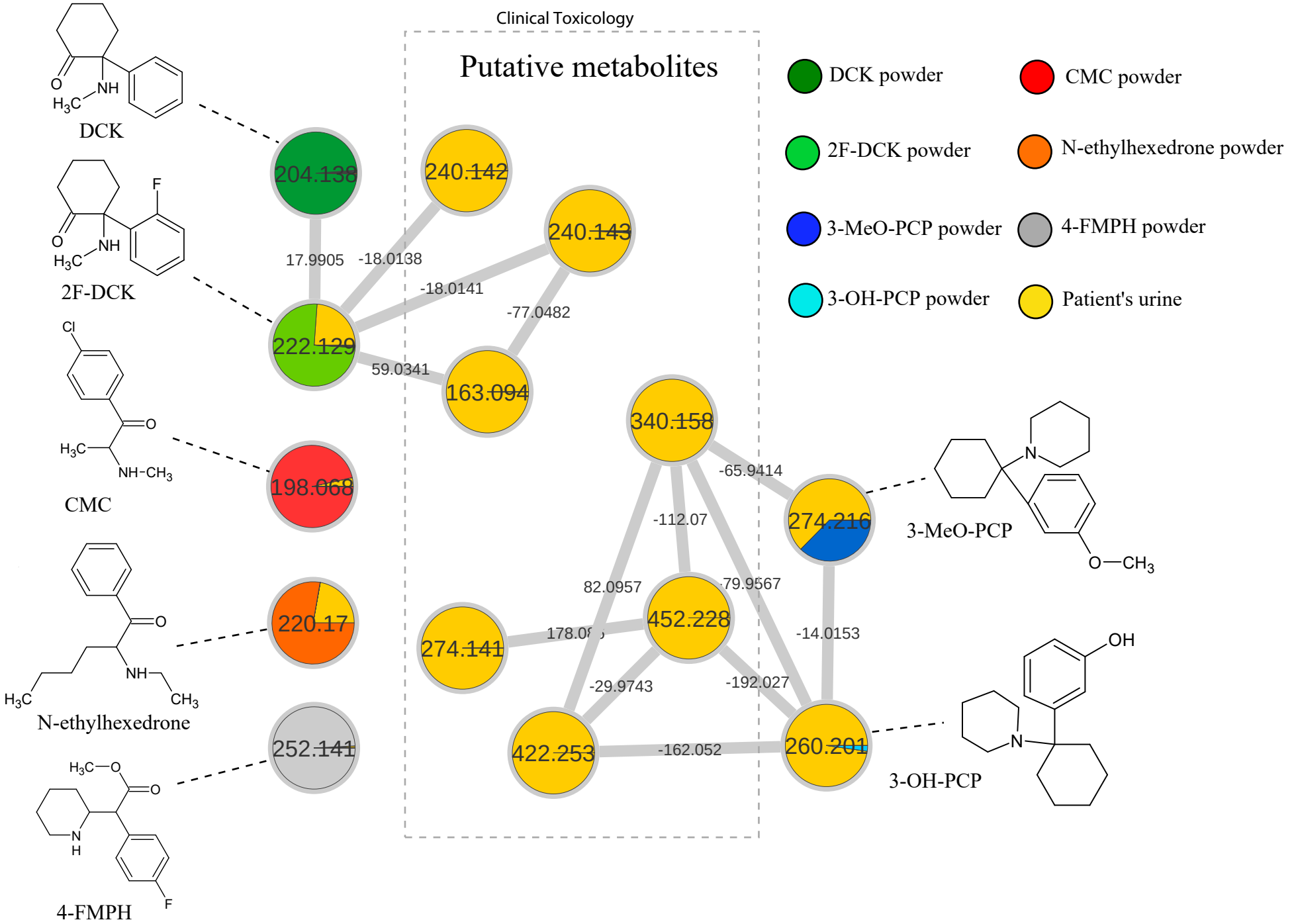
ABSTRACT:

Background: The recreational use of new psychoactive substances (NPS) is increasing worldwide. Among them, the arylcyclohexylamine family including phencyclidine (PCP) and ketamine derivatives is increasing. We report a non-fatal intoxication mainly due to arylcyclohexylamine compounds illustrated by molecular networking.

Case details: a 37-year-old man with a history of drug abuse was discovered with several bags labelled as research chemicals around him and traces of powder on his nose. He was rehydrated, intubated and admitted to the intensive care unit. Urine and drug were analyzed by liquid chromatography-mass spectrometry for NPS identification. Several NPS were quantified in urine: 3-OH-PCP at 12 085 mg/L, 3-MeO-PCP at 1 100 mg/L, 2F-DCK at 147 mg/L, N-ethylhexedrone at 165 mg/L and CMC at 48 mg/L. Using a bio-informatic approach, a molecular network was built to confirm the consumption of powders contained in the bags by comparison with patient's urine.

Discussion: this case illustrates the interest of molecular networking to (i) perform sample-to-sample comparison, (ii) target quantification methods and (iii) allow proper management to confirm the relevance of the treatment.

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The recreational use of new psychoactive substances (NPS) is increasing worldwide. Among them, the arylcyclohexylamine family including phencyclidine (PCP) and ketamine derivatives is increasing and emerging worldwide [1] and also in France [2]. Here, we aimed (i) to describe clinical and biological findings of a rare multiple NPS intoxication involving arylcyclohexylamine derivatives and (ii) to show the interest of molecular networking in the identification of the responsible substances. The case report was approved by the research ethics committee of Rennes University Hospital.

The case was a 37-year-old man with a history of depressive syndrome, opioid addiction, and nasal ketamine, N-ethylhexedrone and other dissociative drug abuse. His usual treatment included mianserine (30 mg/day), extended release lithium (400 mg/day), clomipramine (75 mg/day), and buprenorphine (16 mg/day). He was discovered with several bags labelled as research chemicals around him and traces of powder on his nose. He was rehydrated, intubated and ventilated on etomidate and suxamethonium upon the arrival of the mobile medical emergency unit and then sedated with propofol and midazolam. After being taken in charge by the mobile emergency team, the patient was admitted to the intensive care unit (ICU) (Saint-Malo hospital, France). The patient's clinical and biological parameters during the initial clinical examination and in ICU are summarized in Table 1. The patient did not provide any information about the molecules taken, nor even on the ingested dose.

Urine, drug powders and plasma (at day +4) were sent to our reference toxicology laboratory in order to investigate the illicit drugs and NPS implication in this context. Unfortunately, the plasma sample used for biochemistry parameters (Saint-Malo hospital) was no longer available for NPS quantitation.

Molecular networking (MN) is a bioinformatics tool allowing presentation of untargeted tandem mass spectrometry data under graphical form. Each node represents both the ion and its associated

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fragmentation spectrum. The links between the nodes indicate similarities between spectra. Moreover, MN allows sample-to-sample comparison in a semi-quantitative manner. Our routine toxicological screening is an untargeted method allowing (i) the detection of mass between 150 and 1000 m/z, in positive and negative ionization and (ii) the identification against a library of about 1500 toxicological compounds. As molecular 3 networking method is based on the same principle with a mass range restricted to the only molecules of interest and their known metabolites, we here detected masses between 150 and 450 m/z using only positive ionization. Molecular networking has already proven to be a powerful tool for identifying NPS from drug seizures [3] and biological samples as exemplified with a 3-MeO-PCP intoxication [2]. The comparison of molecular network data obtained from patient's urine and from the seven powders contained in the bags found next to the patient allowed us to confirm the consumption of five molecules: 2F-DCK (2-fluorodeschloroketamine), CMC (chloromethcathinone), N-ethylhexedrone, 3-MeO-PCP and 3-OHPCP (Figure 1). Moreover, other compounds in relation with 2F-DCK, 3-MeO-PCP and 3- OH-PCP have been detected in urine only, which support the possibility of being putative NPS metabolites. Some of them, such as a 3-MeO-PCP glucuronide derivative (m/z 452.228), have already been described in a previous work [2]. In addition, data belonging to DCK (deschloroketamine) and 4F-methylphenidate powders were not identified in the urine matrix. This suggests that there was no recent consumption of these substances. Among these NPS, 2F-DCK, 3-OH-PCP, 3-MeO-PCP are arylcyclohexylamine derivative providing dissociative effects without altering the respiratory function. CMC and N-ethylhexedrone are cathinone derivative close to amphetamines. Little is known concerning pharmacokinetic and clinical effects of these compounds. An altered state of consciousness and tachycardia are the most frequent clinical manifestation observed with PCP-derivatives [4]. Co-intoxication with similar symptoms involving 3-OH-PCP and N-ethylhexedrone have recently been described [5], which emphasis the risk of multiple NPS consumption, as in our original case where an association of five NPS belonging to two different chemical families is reported with a

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clinical and biological description. Since 3-OH-PCP, 3-MeO-PCP, CMC and N-ethylhexedrone were detected at low level (below the limit of quantification) in blood 4 days after intoxication, this allows us to estimate an elimination half-life shorter than 20h.

Given the variety of research chemicals derived from ketamine that are increasingly used for recreational purposes, this case illustrates the interest of molecular networking to (i) perform sample-to-sample comparison, (ii) target quantification methods that we do not routinely use and thus (iii) allow proper management to confirm the relevance of the treatment. This visual modelling, although time-consuming and requiring the management of numerous software programs, facilitates the interpretation and understanding of toxicological analysis results and seems to become a valuable toolbox in the context of intoxication involving NPS.

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	Upon arrival on the intensive care unit (Day 0)	**During admission to the ICU (Day 0; H+6)**	**Hospital discharge (Day +4)**
Clinical presentation	~~Agitated coma with sweating and hypertonia.~~ The patient sweated and was agitated with hypertonia. He clenched his teeth, straightened his head and then relaxed it. Pupils were in mydriasis, and mucous membranes were dry. Cardiological auscultation was without particularity. Pulmonary auscultation showed alternating phases of respiratory pauses and	The patient was normotensive, normocardial. Pupils were in mydriasis, and there was no reaction to painful stimulation. Reflexes were sharp and symmetrical. The heart sounds were regular without murmur or rubbing. Hydroaerobic sounds were rare. No stigma of prolonged grounding and compression point was found. The patient had transient oliguria for 12 hours	The patient was normotensive, normocardial. Calm and adapted awakening with extubation allowed on 27/02 with satisfactory haematosis in ambient air Psychiatrically, the patient did not describe a death wish and was not critical of his drug use. No indication for psychiatric hospitalization was retained after specialized evaluation.
Level of consciousness	Glasgow coma scale was fluctuating between 8 and 10 (Y4.V1.M1-3)	Richmond Agitation-Sedation Scale (RASS) : -5 under sedation	Glasgow coma scale : 15

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Electrocardiogram	Sinus tachycardia with right block at 150 beats per minute	Sinus rhythm was at 86/min, PR interval was at 150 milliseconds, QRS complex was normal, axis and QTc were normal	Normal
Electroencephalogram	-	Symmetrical, poorly reactive tracing, with no sign of epilepsy	-
Brain scan with injection	-	Normal	-
Blood pressure (mmHg)	115/100	-	-
SPO_2 (oxygen saturation)	94%	-	-
FiO2 (fraction of inspired oxygen) with controlled ventilation	-	30%	-
Routine biochemistry	Capillary blood glucose at 1.1 g/L [0.74 – 1.06 g/L]	pH : 7.46 [7.35-7.45], pCO2 : 34 mmHg [35 – 45 mmHg], pO2 : 184 mmHg [80 – 100 mmHg], bicarbonates: 24 mmol/L [23 – 27 mmol/L], lactates: 1.4 mmol/L [< 1.3 mmol/L], CPK: 42,000 IU/L [32 – 308 IU/L] (without creatinine elevation). ASAT was at 5 times normal values without cholestasis or ionic disorder.	No ionic disorder No coagulation abnormalities

Routine toxicology analysis	**Plasma**, Acetaminophen assay and ethanolemia were negative and plasma lithium concentration was 0.08 mg/L [0.5 – 1 mg/L][$] **In urine**, screening found clomipramine, citalopram, mianserine and benzodiazepines (Midazolam, nordazepam) Buprenorphine [*]	-	**Plasma,** Nordazepam at 0.11 mg/L [0.2 – 1.8 mg/L] [*], clomipramine at 0.03 mg/L [0.02 – 0.25 mg/L] [*] Midazolam, nordazepam and mianserine were below the low limit of quantification (LLOQ) [*]
NPS analysis in reference toxicology laboratory	**Urine,** 2F-DCK = 147 mg/L CMC = 48 mg/L 3-MeO-PCP = 1 100 mg/L 3-OH-PCP = 12 085 mg/L N-ethylhexedrone = 165 mg/L [*]	-	**Plasma,** 3-OH-PCP, 3-MeO-PCP, CMC and N-ethylhexedrone were below the LLOQ Absence of 2F-DCK [*]

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Table 1: Clinical and biological parameters of the patient at the arrival of the mobile medical emergency unit and in the intensive care unit. * : LC/MS method, $: immunoassay, [normal range].

Figure 1: Molecular network comparing the urine sample with the powders found near the patient. DCK: Deschloroketamine, 2F-DCK: 2-fluorodeschloroketamine, CMC: chloromethcathinone, 4-FMPH: 4-fluromethylphenidate, 3-MeO-PCP: 3- 6 methoxyphencyclidine, 3-OH-PCP: 3-hydroxyphencyclidine. The molecular network displays spectral high resolution mass spectrometry data acquired during analysis where nodes are labelled with the exact mass of ions corresponding to compounds. Nodes were linked together in clusters according to their spectral similarities. The links between the nodes shows mass shifts that could correspond to biotransformation reactions and can thus lead to the identification of putative metabolites. Using multi-matrix approach, the area of different color in each node represent concentrations of the corresponding compound in each sample in a semi-quantitative manner.

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The authors declare that there is no conflict of interest

Informed consent:

Informed consent was obtained from the patient

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