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3-MeO-PCP intoxication in two young men: First in vivo detection in Italy

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ABSTRACT

3-MeO-PCP or 3-methoxyphencyclidine is a derivative of phencyclidine. It acts as a dissociative anesthetic and it has allegedly hallucinogenic and sedative effects. There are almost no documented intoxication cases and references about its pharmacology and toxicity in literature. This study presents two concomitant intoxication cases due to consumption of 3-MeO-PCP and alcohol. A 19 (A) and a 21 years old (B) men were brought to Santa Maria Nuova Hospital in a comatose state (Glasgow score 3). They showed respiratory acidosis, right anisocoria with mydriatic pupils and hypothermia. Toxicological screening was negative. They were intubated for 7–8 h. Almost 24 h after hospitalization they were still in a delirious and agitated status. The subjects declared a high alcohol consumption and ingestion of unknown pills. Blood and urine were collected upon their arrival to the Emergency Department and sent to our Forensic Toxicology Division. Blood alcohol content was 2.0 g/L for subject A and 1,7 g/L for subject B. The specimens were analyzed by means of GC–MS, revealing the presence of 3-MeO-PCP. A confirmation and quantification was carried out by means of a new and fully validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method for new psychoactive substances (NPS) detection. The analysis was performed adding acetonitrile to the samples, the supernatant was dried and reconstituted with methanol. Mephedrone-D3 was used as internal standard. Acquisition was performed through multiple reaction monitoring (MRM) dynamic mode. The MRM transitions used for quantification of 3-MeO-PCP were: *m/z* 274 → 86, 121. 3-MeO-PCP was quantified in all the biological samples at the following concentrations: 350.0 (blood) and 6109.2 (urine) ng/mL for A; 180.1 (blood) and 3003.6 (urine) ng/mL for B. Taking into account the analytical results, we can suppose that the manifested symptoms were due to the consumption of 3-MeO-PCP in synergy with alcohol. Our report is the first case of 3-MeO-PCP intoxication in Italy and one of the few documented all over the world. For this reason, this case represents a significant worrisome alarm about the spread of this substance. Here we want to highlight the importance of having an effective and broad-spectrum analytical method in order to face the NPS issue.

1. Introduction

Novel Psychoactive Substances (NPS), also known as “legal highs”, “designer drugs” or “bath salt”, are rapidly changing the worldwide drug scene [1]. These compounds are synthetic drugs sold as “legal alternative” to the classic ones. National and Supranational Institutions have implemented many activities to identify these substances in order to schedule them as law controlled substances. NPS spread is mainly due to their relative inexpensiveness, easiness of purchasing (for example on the Internet market) and undetectability with routine drugs screening tests. Toxicological profiles of these substances are very often unknown, with no references about their potential physical or social harm among users. A large number of NPS is currently available (over 1000 different molecules) with a very high structural variety. Several different chemical classes have been detected: synthetic cathinones, synthetic cannabinoids, piperazines, phenethylamines, tryptamines, phencyclidines.

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Phencyclidines class includes analogs and drug substitutes of 1-(1-phenylcyclohexyl)piperidine (PCP), a dissociative anesthetic removed from the market in the 1965 for its hallucinogenic side effects [2]. Over the last years,the spread of the PCP and its derivatives has increased also because they have been brought back on the market in the wake of a drugs "revival trend" [3,4]. Anisylcyclohexylamines are a class of PCP derivatives that include three isomeric form of 1-anisylcyclohexylpiperidine (Fig. 1) described for the first time in 1965 [5] when Maddox et al. published the synthesis of 1-[1-(2-methoxyphenyl)cyclohexyl] piperidine (2-MeO-PCP) and 4-MeO-PCP. The other isomer, 3-MeO-PCP, was later described by Geneste et al. [6] in 1979 (Fig. 1). 3-MeO-PCP is a potent *N*-methyl-D-aspartate receptor (NMDAR) antagonists (Ki = 4.8 nM) [7–9]. This pharmacological activity plays a key role for the dissociative anesthetic effects of 3-MeO-PCP and all the PCP analogs. Few information about the psychoactive effects are available on the scientific literature; on the contrary, a lot of online drug forums extensively describe consumption experiences and the felt effects [2]. The main desired effects are euphoria, empathy, dissociation and hallucinations, while side effects are psychomotor agitation, cognitive impairment and confusion [8,10].

In literature very few intoxication cases due to the consumption of 3-MeO-PCP have been reported. In this paper, we describe the first detection of 3-MeO-PCP in biological fluids in Italy where this molecule is still legal. The specimens were collected from two young men hospitalized after they passed the night drinking and consuming unknown pills. Quantification of 3-MeO-PCP was obtained by means of a new screening method by liquid chromatography–tandem mass spectrometry (LC–MS/MS) that allows the simultaneous detection of 69 compounds (64 NPS and 5 amphetamines) [11]. This new analytical procedure has been developed as our Forensic Toxicology Division is strictly focused on the NPS issue and previous findings [12,13] led us to improve our detection skills setting up this effective and fast procedure.

2. Case presentation

Two young men of 19 (A) and 21 (B) years old were hospitalized at Santa Maria Nuova Hospital in Florence in a comatose state (Glasgow coma score: 3), showing respiratory acidosis, right anisocoria, mydriatic pupils and hypothermia. Subject B had also a nasal fracture. They were intubated with minimal sedation for 7 h. At awakening, patients were still in an altered state, in particular subject A was delirious and euphoric. When they recovered, they declared consumption of high amount of alcohol and ingestion of unknown pills. Neither alcoholic beverages nor pill were found or collected.

At hospitalization, toxicological screening tests were negative for all the common drugs of abuse. Blood and urine samples were collected for each subjects upon their arrival to the Emergency Department and then sent to our Forensic Toxicology Division for the toxicological analysis.

3. Material and methods

3.1. Chemicals

Hydrochloric acid (HCl), methanol (MeOH), acetonitrile (ACN) ammonium hydroxide (NH_4OH), glacial acetic acid and formic acid were acquired from J.T. Baker (Deventer, Holland). Dichloromethane (DCM), toluene, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetaminde (MSTFA), LC–MS CHROMASOLV® MeOH, LC–MS CHROMASOLV® ACN and LC–MS CHROMASOLV® water were purchased by Sigma–Aldrich (St. Louis, MO, USA). Sodium hydroxide (NaOH) and isopropanol were provided by Panreac Quimica S.L.U. (Castellar del Vallès, Spain). 3-MeO-PCP, 4-MeO-PCP and mephedrone-D3 (internal standard, IS) were provided by LGC Standards (Milan, Italy). All standards were diluted to the appropriate concentration with MeOH. Calibration points and quality controls (QC) were obtained spiking aliquots of the same blank blood samples with the appropriate amounts of 3-MeO-PCP and 4-MeO-PCP reference materials. Bond Elut LCR-certify 130 mg solid-phase extraction (SPE) cartridges were obtained from Agilent Technologies (Palo Alto, CA, USA).

3.2. EMIT® immunoassay screening test

Urine samples were analyzed with an EMIT® Siemens VIVA-E drug testing system (Siemens, Newark DE) in order to investigate the common drugs of abuse: cocaine, opiates, cannabinoids, amphetamines, barbiturates, methadone and benzodiazepines according to the manufacturer's instructions.

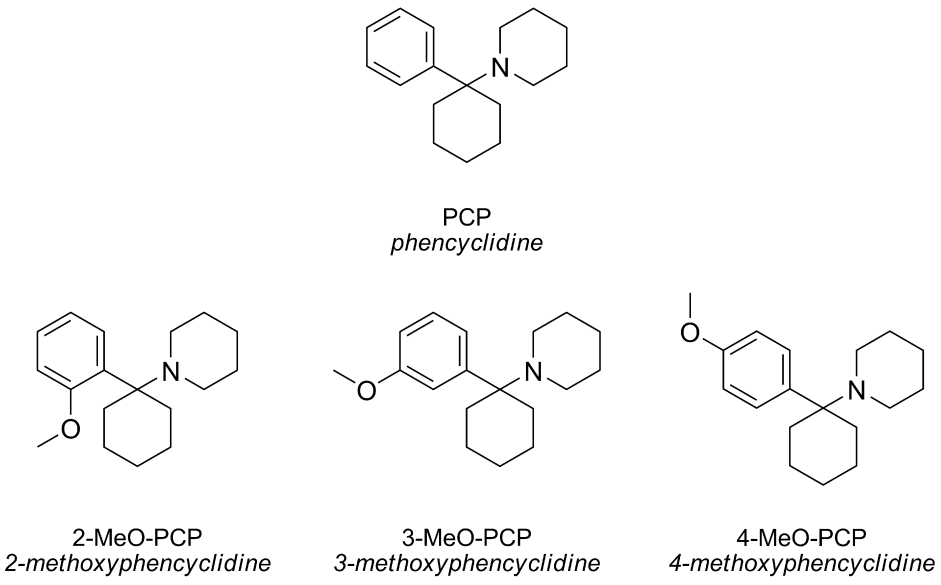

Fig. 1. Chemical structures of PCP, 2-MeO-PCP, 3-MeO-PCP and 4-MeO-PCP.