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A case of non-fatal intoxication associated with the recreational use of diphenidine

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ABSTRACT

Diphenidine is a dissociative drug commonly sold online as research chemical. Several psychotropic effects can appear during diphenidine intoxication including euphoria, shifts in perception of reality, hallucinations and transient anterograde amnesia.

In this study, we report a case of acute intoxication occurring after diphenidine intake.

A 30-year-old Caucasian male was hospitalized after he was found in a confused and agitated state, and unable to communicate. The physical examination displayed tachycardia, miotic pupils and increased body temperature and respiratory rate. GC/MS analysis revealed the presence of diphenidine in plasma and urine at concentrations of 308 and 631 ng/mL, respectively. Plasma analysis also revealed the presence of methylphenidate and diclazepam. The clinical progress of the patient was favourable and his symptoms were cured with a symptomatic treatment.

The combined circumstantial elements and toxicological results of the case reported revealed the occurrence of an acute intoxication ascribable to the recreational abuse of diphenidine.

Diphenidine (1-(1,2-diphenylethyl)piperidine) is a dissociative anaesthetic designer drug structurally related to arylcyclohexylamines like phencyclidine (PCP), ketamine and methoxetamine (MXE) (1). Diphenidine was first synthesized in 1924 and studied as a neuroprotective agent for the treatment of brain injury following hypoxia (2). Diphenidine can act as N-methyl-D-aspartate (NMDA) receptor antagonists, serotonin transporter inhibitors, dopamine agonists and opioid agonist, producing dissociative effects similar to those induced by ketamine and MXE (1,3). For this reason, diphenidine and its analogues are candidated to be used as a recreational drug, mainly among users of new psychoactive substances. All these drugs are available from internet suppliers and sold as research chemicals 'not for human consumption'(4). Diphenidine is generally sold as white or slightly yellowish powder or fine crystals. The most common routes for recreational intake, reported by drug users in web discussion forums, are nasal insufflation (snorting) and oral ingestion (3). Due to the fact that this drug is not used for medical purposes, the information about its pharmacology, side-effects, and toxicology are very limited. In the reports collected on web forums, diphenidine use is associated with strong dissociative effects starting at oral doses of 110 mg and higher doses inducing bizarre somatosensory phenomena and transient anterograde amnesia, lasting for 3–6 h (1).

Recently, Helander et al. described a series of 17 cases of intoxication due to the consumption of diphenidine and methoxphenidine (5). The commonly recorded clinical features were hypertension, tachycardia, anxiety, and altered mental status including confusion, disorientation, dissociation, and/or hallucinations. The same symptoms were reported by Hofer et al. in an intoxication case associated to the use of methoxphenidine (6). A case of acute and lethal intoxication related to the simultaneous consumption of the synthetic cannabinoids AB-CHMINACA, 5-fluoro-AMB and diphenidine were also reported in literature (7). In another study, the post-mortem distribution of these drugs in body fluids and solid tissues was studied and similar cases of acute or fatal intoxication associated with the use of the methoxy-analog of diphenidine, namely 2-methoxy-diphenidine, were recently reported (8). However, little is still known about the correlation between

the blood concentration of these compounds and their effects. In this paper, we report a case of acute toxicity after diphenidine intake, in association with other psychoactive substances. The presence of the drug was confirmed in plasma and urine by means of mass spectrometry-based chromatographic methods.

Case Report

A 30-year-old Caucasian man with previous history of drug addiction was found seated alongside his bed in a confused and agitated state, and unable to communicate. On the floor, a small plastic bag was found, containing few milligrams of a white powder labelled 'Diphenidine 1g'. The content of the plastic bag was analytically confirmed by gas chromatography-mass spectrometry. No current medication was declared to the rescue unit by the subject's relatives. The first physical examination revealed tachycardia (heart rate 160 bpm), and miotic nonreactive pupils. The preliminary medical examination also verified a state of agitation, disorientation and altered consciousness with a Glasgow Coma Scale (GCS) of 9. Midazolam (30 mg intravenously, divided in repeated injections at increasing dosages) was initially administered for sedation. No traces of vomit were found. On arrival at the emergency department, the patient was still agitated and uncontrollable, with major muscular rigidity. The physical examination displayed tachycardia (160 bpm), tachypnea and miotic pupils. The external body temperature recorded was 38.0°C. Blood gas analysis revealed severe metabolic acidosis with blood pH 7.17 (reference 7.35–7.45), base excess (BE) of −14 mmol/L (reference from −2 to +2 mmol/L) and lactate concentration of 13 mEq/L (reference <4mEq/L). The patient was treated for sedation with midazolam (15 mg intravenously), diazepam (10 mg intravenously), chlorphenamine maleate (10 mg intravenously), haloperidol (2 mg intravenously) and sodium bicarbonate 5% m/v (250 mL intravenously). After 90 min, the patient regained consciousness but his speech was still drowsy and slowed. His pupils were still miotic but no amnesia phenomenon was reported. The ECG and the respiratory rate were normal, while the

body temperature was around 37.0 °C. The patient admitted to have taken the diphenidine powder by nasal insufflations about five hours before the rescuer arrival at his home. Twelve hours after the hospitalization, laboratory analysis revealed an increase of creatine kinase (CK: 87923 U/L; reference < 190 U/L), alanine aminotransferase (ALT: 77 U/L; reference < 40 U/L), aspartate aminotransferase (AST: 500 U/L; reference < 37 U/L), and lactate dehydrogenase (LDH: 4908 U/L; reference 240–480 U/L) indicating rhabdomiolysis. After two hours, the blood pressure was reverted to 115/70 mmHg, with an heart rate of 88 bpm and a body temperature back to 36.6 °C. Twelve hours after arrival at the Emergency Department, the patient was relaxed and drowsy, but easily aroused by verbal stimulation. His blood pressure was stable at 125/70 mmHg, with an heart rate of 65 bpm. After 5 days of observation, the patient was discharged. CK, ALT, AST and LDH trends recorded during the hospitalization period are shown in Figure 1. Blood and urine samples were collected on admission and submitted to the laboratory for toxicological analyses. Moreover, an hair lock sample was collected as additional matrix and tested for the presence of several new psychoactive substances with stimulant, psychedelic, and dissociative properties.

Toxicological analysis

Immunochemical toxicology screening on urine was performed by Enzyme Multiplied Immunoassay Technique (EMIT, Abbott Laboratories, IL, USA) and turned out positive for benzodiazepines and cannabinoids, and negative for cocaine, amphetamine, opioids, barbiturates, methadone, tricyclic antidepressants, 3,4-methylenedioxymethamphetamine and methamphetamines. Screening analysis for unknown substances was performed in urine, plasma (both extracted with TBME at alkaline conditions) and the powder found beside the patient at his home by gas chromatography/mass spectrometry. Full scan spectra in the interval 40-650 amu were acquired using a 5975 inert mass-selective detector (Agilent Technologies, Milan, Italy) operating in the EI mode at 70 eV. The qualitative identification of the compounds was performed by

comparing the full scan spectra obtained with those recorded in the updated spectra libraries (PMWTox2, SWGDRUG version 1.7, AAFS2012, CaymanSpectraLib). For the diphenidine confirmation analysis, a dedicated GC-MS procedure was developed. A 6890N gas chromatograph from Agilent Technologies (Milan, Italy) equipped with a J&W HP-5 capillary column, 17 m × 0.200 mm × 0.33 µm was used. Helium was employed as the carrier gas at a constant pressure of 30.00 psi. The GC oven temperature was set at 90°C for 1 min and then raised to 180°C with a 30°C/min heating rate. The oven temperature was maintained at 180 °C for 7 min and then raised to 315 °C with a 15 °C/min heating rate. The total run time was 23 min. The GC injector and transfer line were maintained at 280°C.

The chromatograph was coupled to a 5975-inert MSD from Agilent Technologies (Milan, Italy) with EI at 70 eV. Quantitative determination of diphenidine was performed by monitoring the diagnostic ions at m/z 174 (target ion), 175 and 91 (qualifiers), whereas for the internal standard (ethaverine), the diagnostic ions at m/z 366, 280 and 394 were chosen.

Other confirmation analyses on blood, urine and hair were performed by means of updated liquid chromatography/tandem-mass spectrometry (LC/MS-MS) methods routinely employed in our laboratory (9,10,11,12).

Results

Diphenidine was identified as the only component of the powder. The same compound was quantified in plasma and urine specimens at concentrations of 308 ng/mL and 631 ng/mL, respectively. Moreover, diphenidine was detected in hair sample at 4400 pg/mg concentration. Other findings included α-PVP (1040 pg/mg), MDPV (120 pg/mg), methoxetamine (27 pg/mg), 4-fluoroamphetamine (55 pg/mg) and methylone (traces). Several other drugs were quantitatively determined in plasma, some of which had been administered in hospital. These included benzodiazepines such as diazepam, nordiazepam, delorazepam (chlordesmethyldiazepam),

lormetazepam, lorazepam and midazolam, together with haloperidol and methylphenidate. Moreover, the designer benzodiazepine diclazepam was also found in the patient's plasma sample at a concentration of 3.5 ng/mL. All the findings in plasma and urine samples are summarized in Table 1.

Discussion

Dissociative drugs distort perceptions of sight and sound and produce feelings of detachment (or dissociation) from the environment and self. Among the dissociative drugs, ketamine and phencyclidine (PCP) are the drugs most commonly used for recreational purpose. In the last 5 years, a new generation of synthetic dissociative drugs appeared on the market, including methoxethamine (MXE), methoxphenidine, diphenidine and phencyclidine derivatives (e.g. 4-MeOPCP), which have rapidly spreaded as a legal replacements for the banned ketamine and PCP (1). The introduction of new psychoactive drugs on the market make it difficult to identify the substances responsible for intoxication cases that turn up at the emergency departments. Once identified, very few data are generally available in the literature about these substances, their metabolism, acute and chronic toxicity, and clinical symptoms that they produce. Moreover, the consumers of new psychoactive substances (NPS) frequently combine the intake different type of drugs resulting in unpredictable serious interactions with related clinical signs difficult to interpret.

In a study reporting 17 intoxication cases produced by consumption of diphenidine and methoxphenidine, common adverse symptoms reported were hypertension (systolic blood pressure > 140 mmHg), tachycardia (heart rate > 100 bpm), anxiety, agitation, nystagmus, dilated pupils and muscle rigidity (5). Moreover, altered mental status was sometimes recorded, including modified level of consciousness, hallucinations, confusion, disorientation and dissociation. In another case of acute toxicity associated with the recreational use of methoxphenidine, symptoms such as tachycardia (112 bpm), hypertension (220/125 mmHg), echolalia, confusion, agitation, opisthotonus, nystagmus and amnesia were recognized in the intoxicated patient (6). Moreover, an

increase of blood creatine kinase (max 865 U/L), alanine aminostransferase (72 U/L) and gamma-glutamyl transpeptidase (123 U/L) was also reported.

In the present case, the patient showed symptoms such as agitation, disorientation and altered consciousness state. Moreover, tachycardia, increased respiratory rate, miotic pupils and muscular rigidity were reported and blood analysis revealed signs of metabolic acidosis and rabdomiolysis. All the symptoms observed were compatible with the effects induced by dissociative drugs like MXE, ketamine, PCP and the new diphenidine and methoxphenidine drugs (5,6,13,14). The concentration of diphenidine found in plasma (308 ng/mL) was comparable to those of diphenidine and methoxphenidine in the 17 intoxication cases associated with the consumption of these drugs (2-409 ng/mL; mean: 122 ng/mL; median: 93 ng/mL) (5). This concentration is also 4-80 fold lower than those observed in three fatalities involving methoxphenidine (8). In the patient of the present case, benzodiazepines were administered together with haloperidol for sedation and for the treatment of tachycardia and hypertension. All the other detected substances (excluding methylphenidate and diclazepam) had been used during the therapy in hospital. The simultaneous detection in urine and plasma samples of delorazepam, lormetazepam and lorazepam is compatible with a diclazepam intake, as was demonstrated in a controlled study on diclazepam metabolism (15). In current literature there are very little data on diclazepam levels in biological fluids. The blood concentration found in the presented case (3.5 ng/mL) is comparable to that registered 3 hours after an oral intake of a 1 mg tablet of diclazepam by a 43 years old male subject (weight 73 kg) in a study published by Moosmann et al. (15). Concerning methylphenidate, although the recorded blood concentration (3 ng/mL) was below the therapeutic levels (5-60 ng/mL) (16), a possible synergic stimulant effect in combination with diphenidine cannot be excluded. The detection of diclazepam and methylphenidate in the patient's plasma sample suggests that these drugs have most likely been consumed together with diphenidine or within a restricted period of time, potentially influencing and reinforcing their effects. Designer benzodiazepines are often taken as 'self medication' by users of stimulant and hallucinogenic drugs, leading to 'upper downer

cycles‘ (17). Lastly, the presence of diphenidine, together with α-PVP, MDPV, methoxetamine, 4-fluoroamphetamine and methylone, in the hair sample indicates that the subject had previously been exposed to these drugs in more than one occasion.

In conclusion, diphenidine appears to have acute toxicity similar to that of other dissociative drugs like ketamine, phencyclidine and other new designer drugs, such as methoxethamine and methoxphenidine. Due to the increasing diffusion of these drugs, occasional cases of intoxication from diphenidine consumption are likely to occur, with consequent access to emergency rooms and subsequent hospitalization of the drug users. Despite the lack of data and case reports in the current literature, it is advisable that the whole symptoms are promptly recognized and an adequate treatment is implemented for patients whose intoxication cause cannot be immediately identified.

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Figure 1: trend of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK) and lactate dehydrogenase (LDH) in patient's blood during the period of admission.

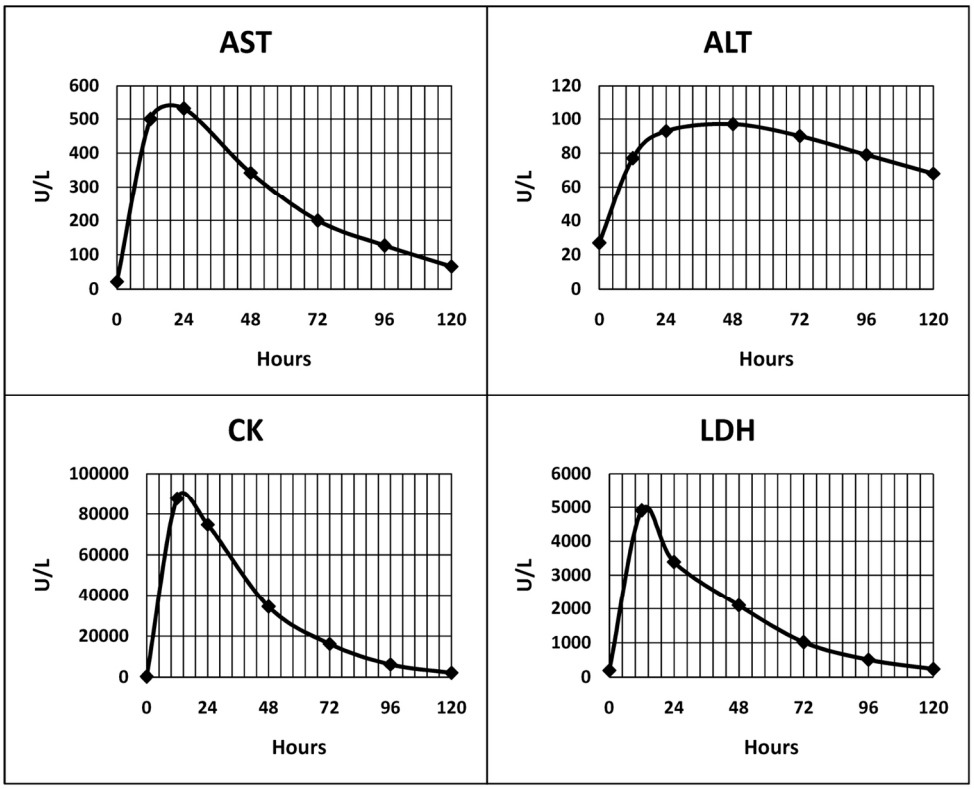

Figure 1
144x115mm (300 x 300 DPI)

Table 1: analytical findings in plasma and urine samples

Analytes	Plasma (ng/mL)	Urine (ng/mL)
Diphenidine	308	631
Diazepam	376	2.0
Nordiazepam	7.0	neg
Temazepam	3.6	neg
Diclazepam	3.5	neg
Lormetazepam	2.4	345
Delorazepam	45	71
Lorazepam	5.1	212
Midazolam	214	73
Haloperidol	4.0	n/p
Methylphenidate	3.0	<LOQ
THC metabolite*	neg	120

*11-nor-9-carboxy-delta-9-tetrahydrocannabinol
n/p: analysis not performed