Mini review

3,4-Methylenedioxypyrovalerone (MDPV): Chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online

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\textbf{Abstract}

The illicit marketplace of substances of abuse continually offers for sale legal alternatives to controlled drugs to a large public. In recent years, a new group of designer drugs, the synthetic cathinones, has emerged as a new trend, particularly among young people. The 3,4-methylenedioxypyrovalerone (MDPV), one of this synthetic compounds, caused an international alert for its cardiovascular and neurological toxicity. This substance, sold as bath salts, has caused many serious intoxications and some deaths in several countries. The aim of this paper is summarise the clinical, pharmacological and toxicological information about this new designer drug.

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\section*{1. Introduction}

The illicit marketplace of substances of abuse continually offers for sale legal alternatives to controlled drugs to a large public. These psychoactive substances are both synthetic derivatives and vegetable compounds that can produce important public health consequences and policy implications (Collins, 2011). Furthermore, the internet has emerged as a new marketplace for the spread of these products and its monitoring is an important instrument to identify new trends of drugs of abuse (Schifano et al., 2010). Recent information have shown that the online market is able to respond rapidly to changes in the legal status of the psychoactive drugs offering for sale new legal alternatives (Walsh, 2011).

After the development of synthetic derivatives based on fentanyl in the 1980s, ring-substituted phenethylamines in the late 1980s, tryptamines in 1990s and piperazines in the 2000s, in recent years, a new group of designer drugs, the synthetic cathinones, has emerged as a new trend, particularly among young people (Brandt et al., 2010). Synthetic cathinones are a group of synthetic derivatives of the vegetable cathinone, a phenylalkylamine...
alkaloid naturally present in the Catha edulis (khat) (Hassan et al., 2007). The first synthetic cathinone which has had a large diffusion in the population was the mephedrone, a psychoactive substance that has produced many serious intoxication and some deaths in various countries (Hadlock et al., 2011). When the legal status of this compound changed, another synthetic cathinone, the 3,4-methylenedioxyxypyrovalerone (MDPV), received a large diffusion among young people causing a new international alert (ISS, 2011). The aim of this paper is summarise the clinical, pharmacological and toxicological information about this new designer drug.

2. Synthetic cathinones, Catha edulis (khat) and natural cathinones

2.1. Synthetic cathinones

Synthetic cathinones are the beta-keto analogues of the natural cathinone, one of the psychoactive compounds present in khat, in particular, most of the synthetic cathinones appeared in the recreational drug market since the mid-2000s are a ring-substituted cathinone closely related to the phenethylamine family, differing only by a keto functional group at the beta carbon (namsdl, 2011). Like the related phenethylamines, synthetic cathinones can exist in two stereoisomeric forms that may have different potency and it is likely that some ring-substituted derivatives could be racemic mixtures (Gibbons and Zloh, 2010). Synthetic cathinones produce amphetamine-like effects because they inhibit the reuptake of and stimulate the release of norepinephrine, serotonin and dopamine (Cozzi et al., 1999; Kehr et al., 2011). These molecules are used as substitute for other stimulants such as amphetamines, cocaine or ecstasy because, although they are generally less lipophilic and less able to cross the blood–brain barrier (pyrrolidin derivatives such as pyrovalerone or MDPV are more lipophilic and more able to cross the blood–brain barrier than other synthetic cathinones), they can produce the same effects on the Central Nervous System (Dargan et al., 2011). The studies on the metabolism of cathinone derivatives in rats and humans have shown that they are N-demethylated, the keto group is reduced to hydroxyl and ring alkyl groups are oxidised (Meyer and Maurer, 2010). The users can snort or ingest these white or brown amorphous or crystalline powders, but since they are soluble in water, these substances can also be injected (Winstock et al., 2011; Schifano et al., 2011). In recent years, the assumption of synthetic cathinones has been associated with several cases of toxicity and deaths (James et al., 2010). Clinical features include neurological, cardiovascular and psychopathological symptoms such as: psychomotor agitation, delusions, hallucinations, psychosis, hypertension, palpitation, chest pain, seizures, headaches (Wood et al., 2010). Synthetic cathinones include several substances that have been used as research chemical, but only three compounds are used as medicinal products: amfepramone (obesity), pyrovalerone (obesity and chronic fatigue) and buproprion (depression and tobacco dependence), the others are used only for recreational scope (pharmacycode-amfepramone, 2011; pharmacycode-bupropion, 2011; Gordons and Cole, 1971).

2.2. Chatha edulis (khat) and natural cathinones

Catha edulis, simply called khat, is an evergreen slow-growing shrub or tree native to Ethiopia and cultivated in East Africa and South West Arabian Peninsula that in recent years has been widespread in Europe too (emcdda, 2011). The people living in khat geographical areas use the fresh vegetable material (leaves, stems, flower buds) of this plant for its stimulant effects (Kalix, 1992). The fresh khat leaves contain 62 alkaloids and for two of these, cathine and cathinone, have been demonstrated amphetamine-like effects, particularly, these phenylalkylamine alkaloids cause the release of catecholamines from pre-synaptic storage sites in the central and peripheral nervous system (Kalix, 1986). In addition, these alkaloids may also have monoamine oxidase inhibition effects (Nencini et al., 1984). Cathine and cathinone determine in humans increased blood pressure and in heart rate, euphoria and psychomotor hyperactivity (Brenneisen et al., 1990). Several studies have shown the harmful effects of this plant such as: increased incidence of acute coronary vasospasm and myocardial infarction, oesophagitis, gastritis, oral keratotic lesions and liver toxicity (Al-Habori, 2005). Furthermore, insomnia, depression, anorexia, psychosis and impaired working memory have been reported after occasional or chronic use of khat (Balint et al., 2009; Colzato et al., 2011).

3. 3,4-Methylenedioxyxypyrovalerone (MDPV)

3.1. Chemistry

The MDPV is a pyrrolidine derivative of the synthetic cathinone pyrovalerone differing for the presence of a 3,4-methylenedioxy group linked to the aromatic ring in substitution of a 4-methyle group (Yohannan and Bozenko, 2010) that was synthesized by Boehringer Ingelheim and patented in 1969 and first seized in Germany in the year 2007 (Westphal et al., 2009). This compound, IUPAC name 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylpentan-1-one, is a white (HCL salt form), brown or yellow-green (free base form) or gray (European form) amorphous or crystalline powder with a molecular weight of 275.34284 g/mol classified as a research chemical (PublicChem, 2011). The MDPV includes in its chemical structure a nitrogen atom attached to three carbon atoms composing a tertiary amino group that is responsible of the high solubility of this compound in organic solvents, in particular the free base (CaymanChem, 2011).

3.2. Pharmacology

Like pyrovalerone, MDPV is a monoamine uptake inhibitor more lipophilic and more potent than other cathinone derivatives (Meltzer et al., 2006). The high lipophilicity of this substance is caused by the pyrrolidine ring and the tertiary amino group creating a less polar molecule more able to cross the blood–brain barrier (Emcdda, 2010). The metabolism of MDPV was evaluated in vitro using human liver microsomes and S9 cellular fractions for CYP450 phase I and uridine 5-diphosphoglucuronosyltransferase and sulfotransferase for the phase II metabolism. This study has demonstrated that the main metabolites of MDPV are catechol and methyl-catechol pyrovalerone which are in turn sulfated and glucuronated (Strano-rossi et al., 2011).

3.3. Toxicology

There are limited information about the short and long-term toxicological effects of this designer drug of abuse. The action of MDPV on monoamine reuptake may produce stimulant effects like cocaine, amphetamines or ecstasy, particularly, the stimulant effect has been compared to methylphenidate, at low doses, and like cocaine, amphetamines or ecstasy, particularly, the stimulant effect has been compared to methylphenidate, at low doses (Scribd, 2011). In literature there have been reported acute toxicity episodes and deaths related to MDPV assumption in several countries (Acep, 2011). Acute toxicity mainly includes neurological, cardiovascular and psychopathological symptoms such as: tachycardia, chest pain, S-T segment changes, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, parkinsonism, delusions, hallucinations, paranoid psychosis, depression, panic attacks,
long term changes in cognition and emotional stability, rhabdomyolysis, abdominal pain, vomiting, kidney damage (Durham, 2011; CDC, 2011; Penders and Gestrin, 2011). The treatment generally includes low or moderate doses of a benzodiazepine to control the signs of toxicity and antipsychotics or propofol when this medication is ineffective (Spiller et al., 2011). Furthermore, it was reported the development of craving, tolerance, dependence and withdrawal syndrome after the frequent consumption of high doses of MDPV (CDC, 2011). The MDPV is not detected via standard drug tests but it is required the gas chromatography/mass spectrometry (GS/MS) (Ojanpera et al., 2011).

4. Internet information

The online discussion about MDPV seems begun around 2004, but the popularity of this substance increased in late 2008 (drugguide, 2011; drugs-forum, 2011). Users reported soft Central Nervous System stimulant effects of MDPV at low doses, but very strong stimulant effects at high doses, more potent than cocaine or amphetamines (drugs-forum, 2011; erowid, 2011). There were many reports of people that have used low doses of MDPV to increase the concentration, capacity to work or study, sexual performance (drugs-forum, 2011; erowid, 2011). Other desired psychoactive effects include: increased sociability, energy, limited euphoria, mild empathogenic effects (drugrecognitionexpert, 2011). Users also reported untoward effects such as: prolonged panic attack, tremor, agitation, insomnia, nausea, headache, tinnitus, dizziness, increased heart rate, altered vision, confusion, suicidal thoughts, anhedonia, depression, psychosis, risk of tolerance and dependence (drugs-forum, 2011; erowid, 2011; zoklet, 2011). Internet information also reported some discussion about the combination of MDPV with other drugs in order to reduce the harmful effects or enhance the desired effects. In particular, the most discussed combination are between MDPV and alcohol, propanol or other beta blocker (to counteract tachycardia) GHB, 5-Meo-MiPT (as an aphrodisiac), GBL, zopiclone (to produce visual hallucinations), kratom, hallucinogens, amphetamines (to enhance stimulant and entactogen effects), pregabalin, fatmolidine, opomazol, domperidone (to counteract stomach pain), opiates (speedball-like effects), cannabis, benzodiazepines (to counteract anxiety) and other synthetic compounds (e.g. maphedrone, methylene) (drugs-forum, 2011). The modalities of administration include: oral ingestion, sublingual, intravenous, intramuscular, smoking, insufflation (snorting), inhalation and it has been reported the rectal administration (drugs-forum, 2011; erowid, 2011). Independently of the modalities of intake, the psychoactive effects may be the same, but non-oral assumption could produce shorter duration of action (drugs-forum, 2011). Some users suggest that 1 mg or 2 mg of MDPV are able to produce psychoactive effects (sublingual, rectal or inhalation assumption), but the typical doses range appear to be between 5 and 30 mg in a single ingestion. Redosing in a single session is very common because MDPV have a short duration of action (doses higher to 200 mg in a single session have been reported) (drugs-forum, 2011; bluelight, 2011; erowid, 2011).

5. Legal status

The MDPV in not approved as therapeutic drug and it is a controlled substance in Sweden (2010), Denmark (2009), Ireland (2010), United Kingdom (2010), Germany (2010), Australia (2010), Finland (2010), Israel and Italy. In addition this substance is controlled in some States of United States of America such as: Alabama, Florida, Idaho, Louisiana, Michigan, Mississippi, New Jersey, North Carolina, North Dakota and Utah (2011) (sostanzine.info, 2011; drugs-forum, 2011).

6. Discussion

The MDPV is a cathcholamines reuptake inhibitor derived by pyrovalerone with strong stimulant effects. This compound, classified as research chemical, can be considered a new designer drug of abuse. Little is known about the clinical, pharmacological and toxicological effects of MDPV, but some reports and the information on drugs forum suggest that its stimulant action could be more potent than cocaine or amphetamines. These psychoactive effects may justify the widespread of this compound as recreational drug, particularly among young people. Furthermore, the legal status of MDPV in several countries, the wide availability on the online market and the difficulty of identification in biological materials have favored the use of this synthetic cathinone as alternative to other illicit stimulants. Finally, the marketing of MDPV as bath salts or plants fertilizer provided false assurances on the safety of this substance as drug of abuse. The literature data and internet information have shown the high Cardiovascular and Central Nervous Systems acute toxicity of MDPV related to the powerful stimulation of the catecholaminergic system (Meltzer et al., 2006; Durham, 2011). Furthermore, the dopaminergic stimulation in the reward system could explain the development of tolerance, abuse, dependence and withdrawal syndrome reported by users (Ross and Peselow, 2009). Thus, considering the limited information about the clinical, pharmacological and toxicological effects of this substance in combination with the potential health risks, the alertness of scientific community is of great importance in order to monitoring and prevent the spread of MDPV.

7. Conclusion

In this paper we reviewed literature data and internet information about the clinical, pharmacological and toxicological effects of MDPV. Although this substance is marketed as bath salts or plants fertilizer, the drug users utilize the MDPV for its cocaine and amphetamine-like effects. Furthermore, in several countries MDPV is a legal alternative to illicit stimulants used by people that are afraid of the judicial consequences of the controlled substances assumption. Clinical reports and internet information clearly demonstrate the acute Cardiovascular and Central Nervous Systems toxicity of MDPV in combination with the high risk of death drug-related, abuse, tolerance and dependence. Scientific community must monitorate the diffusion of MDPV and it should use the information on drugs forum to identify new trends of substances of abuse early. In conclusion, the data currently available suggest that the recreational use of MDPV must be considered highly dangerous to public health.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References


