

COMMENTARY

Methylone and mCPP, two new drugs of abuse?

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Abstract

Recently, two new ecstasy-like substances, methylone and mCPP, were found in street drugs in the Netherlands by the Drugs Information and Monitoring System (DIMS). Methylone (3,4-methylenedioxymethcathinone) is the main ingredient of a new liquid designer drug that appeared on the Dutch drug market, called 'Explosion'. mCPP (meta-chlorophenylpiperazine) is a substance often used as a probe for the serotonin function in psychiatric research, and has now been found in street drugs, both in tablets and powders. Methylone as well as mCPP act on monoaminergic systems, resembling MDMA (3,4-methylenedioxymethamphetamine), with mCPP mainly affecting the serotonin system. The subjective effects of both new substances exhibit subtle differences with those of MDMA. Only little is known about the harmfulness of both methylone and mCPP. However, because of similarities between these substances and MDMA, risks common to MDMA cannot be excluded.

Introduction

Ever since ecstasy (XTC, MDMA) was classified as a Schedule I drug, people have been trying to find non-scheduled alternatives with effects matching those of ecstasy. Examples of such ecstasy-like designer drugs are 4-MTA (Winstock et al., 2002), MBDB (Carter et al., 2000) and MDEA (Freudenmann & Spitzer, 2004). Recently, two new ecstasy-like substances, methylone and mCPP, were detected in street drugs in the Netherlands by the Drugs Information and Monitoring System (DIMS). DIMS is a toxicoepidemiologic monitor of illegal drug markets. Its main focuses are to identify the compounds of synthetic drugs, describe prevalence and trends, and identify health risks (Spruit, 2001).

3,4-Methylenedioxymethcathinone: methylone

At the end of 2004, a new designer drug called 'Explosion' appeared in the Netherlands. This new drug is sold as a liquid via the internet and in Dutch 'smartshops', stores selling non-scheduled (herbal) psychoactive substances. The product is advertised as a 'room odorizer' and is sold in plastic tubes containing 5 ml of liquid. The tubes cost between €10 and €15 (\$13–\$20) and do not present any information about the composition of Explosion; they contain only a label saying 'Room odorizer Vanilla. Do not ingest' and 'Keep away from children. Never use more than one bottle'. In spite of this label, users mention that they ingest the liquid to reach the

intended psychoactive effect. The text was probably put onto the label to circumvent Dutch regulations for illicit drugs and psychoactive substances.

Analyses of Explosion have demonstrated that the main ingredient of the liquid is the compound methylone (3,4-methylenedioxymethcathinone or 2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one). 3,4-Methylenedioxymethcathinone (MDMCAT or MDMC) is the benzylic ketone analogue of 3,4-methylenedioxymethamphetamine (MDMA): it contains an additional oxygen atom at the benzylic position of the molecule (Figure 1) (Cozzi et al., 1999). 3,4-Methylenedioxymethcathinone was first synthesized by Alexander Shulgin. Because of the similarity of effects between methamphetamine and its benzylic ketone methcathinone, he examined whether there was a comparable connection between MDMA and its benzylic analogue. He called the new substance methylone (Cognitiveliberty.org).

Methylone resembles MDMA in its behavioural profile, as methylone substitutes for MDMA in rats trained to discriminate MDMA from saline. Methylone does not substitute for amphetamine or for the hallucinogenic DOM in animals trained to discriminate between these drugs and saline (Dal Cason et al., 1997). Further, also in common with MDMA, methylone acts on monoaminergic systems. *In vitro*, methylone is threefold less potent than MDMA at inhibiting platelet serotonin accumulation and as potent as MDMA in its

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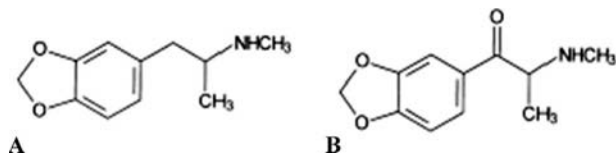


Figure 1. Molecular structures of 3,4-methylenedioxymethamphetamine (MDMA) (a) and methylone (b).

inhibiting effects on the dopamine and noradrenaline transporters (Cozzi et al., 1999).

In spite of these behavioural and pharmacological similarities between methylone and MDMA, the observed subjective effects of both drugs of abuse are not completely identical (Erowid.org). Shulgin wrote about the effects of this drug: 'methylone has almost the same potency of MDMA, but it does not produce the same effects. It has an almost antidepressant action, pleasant and positive, but not the unique magic of MDMA' (Cognitiveliberty.org).

In the Netherlands, methylone is not yet scheduled as a drug of abuse, but is considered to be a psychoactive medicine. Because methylone is not registered officially, as such, it is forbidden to trade in methylone. The Minister of Health has asked the Coordination point Assessment and Monitoring new drugs group (CAM) to gather information about this substance, resulting possibly in an official risk assessment (van Amsterdam et al., 2004). Until now, no research has been conducted on the toxicity of methylone, so nothing is known about the harmfulness of this new drug.

Meta-chlorophenylpiperazine: mCPP

In September 2004, another ecstasy-like drug appeared on the Dutch drug market: meta-chlorophenylpiperazine (mCPP). mCPP is a pharmacologically active metabolite of the antidepressant drugs trazodone, nefazodone and etoperidone and of the minor tranquillizer mepiprazole (Rotzinger et al., 1998). Its chemical name is 1-(3-chlorophenyl)piperazine and the chemical formula is $C_{10}H_{13}ClN_2$ (Reynolds, 1996).

From September 2004 until April 2005, DIMS registered mCPP 25 times in drugs sold mainly as ecstasy, both in tablets and powders. Two different kinds of tablets containing mCPP were found: a beige-coloured, round-shaped tablet and a white tablet with coloured flecks, both types without a logo. The dose of mCPP in the tablets ranged from 2 to 46 mg. In three cases, mCPP was discovered in a powder. Two powders were sold as cocaine and one as speed, containing 7%, 8% and 5% mCPP, respectively, the first-mentioned in combination with 1% cocaine-HCl. In addition to these identifications of mCPP in the Netherlands, mCPP has also been detected in several other European countries. Notifications of the detection of mCPP were received from Sweden, France, Austria and Lithuania, via the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Further, mCPP can be bought on the internet as X4, a tablet containing a combination of four types of piperazines (mCPP, TFMPP, oMPP and pCPP) (Natuurendroger.nu; Modernatur.nu).

mCPP is the most extensively used probe of serotonin function in psychiatric research (Kahn & Wetzler, 1991). It has both pre- and postsynaptic effects on the serotonin system.

First, mCPP induces a release of serotonin (5-HT) dependent on the serotonin transporter (SERT) (Pettibone & Williams, 1984; Baumann et al., 1993, 2001; Eriksson et al., 1999; Gobbi et al., 2002). Secondly, mCPP possesses agonist properties at some 5-HT receptors (e.g. 5-HT_{2C}) and antagonist properties at others (e.g. 5-HT_{2B}) (Hamik & Peroutka, 1989; Thomas et al., 1996; Gijsman et al., 2004). Concerning these effects on the serotonin system, mCPP is a substance partially comparable with MDMA, as MDMA releases 5-HT via a SERT-mediated process as well (e.g. Rudnick & Wall, 1992; for a review see Cole & Sumnall, 2003). As a consequence, the subjective effects of mCPP and MDMA are also comparable, both positive as well as negative (Tancer & Johanson, 2001, 2003). Examples of mild side effects mentioned after the use of mCPP are anxiety, dizziness and confusion (Gijsman et al., 1998; Tancer & Johanson, 2001, 2003; Feuchtl et al., 2004), whereas migraine and panic attacks are observed frequently as severe negative effects (Gijsman et al., 1998, 2004). Interestingly, MDMA-users (McCann et al., 1999) and cocaine addicts (Buydens-Branchey et al., 1997) report a more positive response to mCPP than non-drug using volunteers.

An important difference between mCPP and MDMA is the effect on the dopamine system: mCPP only exhibits minimal effects on this system (Baumann et al., 2001; Gobbi et al., 2002). Therefore, mCPP does not display any reinforcing effects (Tancer & Johanson, 2003). Probably, in contrast with MDMA, heart rate, blood pressure and body temperature are only mildly increased following the use of mCPP (Ghaziuddin et al., 2003; Tancer & Johanson, 2003), while both mCPP and MDMA cause a dose-dependent elevation of the hormones ACTH, cortisol and prolactin (Kahn & Wetzler, 1991; Gijsman et al., 1998; Ghaziuddin et al., 2003; Feuchtl et al., 2004). Physiological and subjective effects reach their peak after 1–2 hours after oral administration (Tancer & Johanson, 2001, 2003). The effects can last 4–8 hours (Gijsman et al., 1998; Tancer & Johanson, 2001, 2003).

While MDMA is known to be a neurotoxic compound, mCPP lacks neurotoxic potential (Gobbi et al., 2002). mCPP is able to release 5-HT without causing a long-term depletion of 5-HT (Ulrichsen et al., 1992; Baumann et al., 2001). Possibly, this difference between MDMA and mCPP can be explained by the fact that mCPP releases only the cytoplasmic 5-HT, while MDMA induces the release of both cytoplasmic and vesicular 5-HT (Gobbi et al., 2002).

The doses of mCPP found in the street drugs analysed by DIMS (2–46 mg) are comparable with the doses used in challenge tests of the serotonin system in psychiatry. In these tests, the commonly used oral dose of mCPP ranges from 0.1 to 0.75 mg/kg (7–52.5 mg mCPP for a 70-kg person) (Tancer & Johanson, 2001, 2003; Gijsman et al., 2004). However, these are doses of individual tablets. When several tablets are ingested, the clinically used dose can be exceeded. This might result in the serotonin syndrome (Klaassen et al., 1998). Therefore, the use of mCPP in combination with alcohol, ecstasy or antidepressant drugs should be avoided.

In contrast with methylone, mCPP is registered officially. Consequently, only licensed traders are allowed to sell this substance. Because mCPP has appeared on the illegal drug market, it might become subject to an official risk assessment by the CAM.

Until now, little has been known about the use and use patterns of methylone and mCPP. Monitoring and specific epidemiological research among high-risk users could gain an insight into risks associated with the use of these drugs alone or in combination with other drugs.

The abuse of methylone and mCPP have not yet been reported to be associated with fatal or non-fatal intoxication. However, both substances carry potential risks common to MDMA and 4-MTA. Therefore, a risk of acute or chronic toxicity cannot be excluded.

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