mCPP: an undesired addition to the ecstasy market

MG Bossong Drug Information and Monitoring System (DIMS), Trimbos Institute for Mental Health and Addiction, Utrecht, The Netherlands.
J Hoek DeltaLab, Albrandswaardsedijk 74, Poortugaal, The Netherlands.
HMJ Goldschmidt DeltaLab, Albrandswaardsedijk 74, Poortugaal, The Netherlands.
RJM Niesink Drug Information and Monitoring System (DIMS), Trimbos Institute for Mental Health and Addiction, Utrecht, The Netherlands.

Abstract

A new ecstasy-like substance, meta-chlorophenylpiperazine (mCPP), has been detected in street drugs in the Netherlands. Theoretically, mCPP possesses the potential to become a non-neurotoxic alternative for methylenedioxymethamphetamine (MDMA), the regular psychoactive substance of ecstasy. Since its introduction on the Dutch market of synthetic drugs, the percentage of mCPP-containing tablets has increased, including both tablets that contain only mCPP and tablets containing a combination of mCPP and MDMA. These tablets occur in many different colours, shapes and sizes and with various logos, making it impossible to distinguish mCPP-containing tablets from regular MDMA tablets. In addition, the reports of users concerning the effects of mCPP are predominantly negative. All these aspects together lead to the conclusion that mCPP is an undesired addition to the ecstasy market from the user’s perspective.

Key words
drug monitoring; ecstasy; mCPP; MDMA; piperazine; toxicity

Introduction

The use of ecstasy is popular, especially with young adults (National Drug Monitor, 2006; European Monitoring Centre for Drugs and Drug Addiction, 2007). This is largely due to the dual effect of the psychoactive substance in ecstasy: methylenedioxymethamphetamine (MDMA). MDMA induces both stimulant and strong empathetic feelings (Baylen and Rosenberg, 2006). Because MDMA is an illegal drug worldwide, people have tried to mimic this popular combination of effects with other, non-illicit substances. Examples of these MDMA-like substances are 4-methylthioamphetamine (4-MTA) (Winstock, et al., 2002) and 3,4-methylenedioxethylampheta mine (MDEA) (Freudenmann and Spitzer, 2004). However, after the introduction of these non-illicit kinds of substances on the ecstasy market, these drugs usually are controlled under drug laws. Thereby, they acquire the same illegal status as MDMA. As a consequence, most substances introduced as alternatives for MDMA ultimately disappear from the market, leaving MDMA unequalled as the favourite party drug. In some cases, for example, with MDEA, the substance originally launched as an alternative for MDMA does not succeed as a party drug independently, but ends up in ecstasy tablets as an additional substance, usually in combination with MDMA (Parrott, 2004).

In September 2004, a new ecstasy-like substance called meta-chlorophenylpiperazine (mCPP) was detected in street drugs in the Netherlands by the Drug Information and Monitoring System (DIMS) (Bossong, et al., 2005). DIMS is a toxicoepidemiologic monitor of illegal drug markets, and its main...
focuses are to identify the compounds of synthetic drugs, to describe prevalence of drugs on the market and trends in drug use and to identify health risks for drug users (Spruit, 2001). mCPP was introduced as an alternative for ecstasy, exerting similar effects as MDMA on the serotonergic system (Rudnick and Wall, 1992; Eriksson, et al., 1999). In addition, the subjective effects of mCPP are believed to be comparable with those of MDMA (Tancer and Johanson, 2001, 2003). However, the most important property of mCPP making it a suitable alternative for MDMA is its lack of neurotoxic potential. Although MDMA is appreciated for its unique spectrum of effects, reservations exist regarding its supposed neurotoxic properties (see for a review Gouzoulis-Mayfrank and Daumann, 2006). One of the leading hypotheses explaining the mechanism of MDMA-induced neurotoxicity is that in case of MDMA-induced serotonin depletion, dopamine can be taken up in the serotonergic axon through serotonin transporters, ultimately resulting in axonal damage (Sprague, et al., 1998). mCPP lacks a neurotoxic potential because it does not cause a long-term depletion of serotonin and it has only a minimal effect on the dopamine system (Baumann, et al., 2001; Gobbi, et al., 2002). Therefore, mCPP, resembling the effects of MDMA but lacking its neurotoxic potential, could be a possible alternative for MDMA.

In the past, several MDMA-like substances were put out on the market, but none of them attained the status of a party drug on its own. Possibly, mCPP is another example of such a failed ecstasy-like designer drug, but in the first few months after the detection of mCPP by DIMS, nothing could be stated about the position of mCPP on the ecstasy market on the long term (Bosson, et al., 2005). In this study, we answer the question whether mCPP has become a new drug of abuse. Therefore, we describe the development of mCPP on the drug market in the Netherlands since its appearance in September 2004 until December 2007. Furthermore, we describe the reported effects experienced by users of mCPP.

Methods

Collection of drug samples

All drug samples were collected by DIMS. DIMS is constituted of a large network of institutions for addiction care within the Netherlands. The coordinating and steering centre is at the Trimbos Institute, the Netherlands Institute of Mental Health and Addiction in Utrecht. The participating institutes are located throughout the country and they provide the possibility for clients to have their drugs tested anonymously in the so-called test offices, situated in the institutes. Personnel working in these offices are trained in providing information on drugs and they handle the communication with the (potential) drug consumers who hand in their drug samples. These samples are coded, and information regarding the drugs, such as logo, colour, diameter, thickness and relevant market or consumer information, is assembled into a database. Most of the drug samples are sent to a laboratory for chemical analysis. Within five days, the laboratory results are put out on a secure Web site that is only available to those participating in DIMS. Drug consumers are orally informed on the compounds of the drug samples they personally delivered. All procedures are carried out according to standardised quality protocols.

This drug testing system enables scientists at the central DIMS office to monitor synthetic drug markets by gathering and interpreting the information from the offices. Furthermore, because of the personal contact with drug users, information is gathered on the subjective effects of a certain drug, the usual dose taken, the frequency of use, etc. When new substances are detected, efforts to elucidate the profile of drug use and its effects are intensified. All these data can be used to base on policy or, in the case of extraordinary health risks, for the purpose of national warning campaigns (Keijser, et al., 2008). More elaborate information on DIMS can be found in the study by Spruit (2001).

Chemical analysis of drug samples

After crushing and homogenising the sample, three analytical techniques were used for identification and quantitation of mCPP. First, thin layer chromatography (Toxilab®A) was performed for identification. Therefore, a small part of the sample (approximately 2 mg) was concentrated on a Toxidisc®, placed in the chromatogram and developed according to the Toxilab®A procedure. The analytes were identified by relating their position (RF) and colour to standards through four stages of detection. mCPP was typically identified with RF 0.27 and was without colour in colouring stage I (Marquis), showed a vanishing red spot in stage II (wash step with water), did not show fluorescence in stage III (UV) and caused a brown spot in stage IV (Dragendorff’s reagents). Subsequently, the quantitation of mCPP was performed with gas chromatography-nitrogen-phosphorous detection (GC-NPD) (Interscience GC8000/NP-800), using 1 μL sample. An internal standard (Chiral, Sigma-Aldrich, Zwijndrecht, The Netherlands) was added to a solution of 0.01 M HCl and this solution was sonicated. An extraction using Toxitubes®A was performed and after 5-times dilution in hexane, the upper layer was injected on the GC-column (WCOT-CP-Sil-8- CB, length 25 m, id 0.32 mm df 0.25 μm). A cold on-column injection was used with a detector temperature of 300 °C and with nitrogen-phosphor-detector and helium as carrier gas. The total run time was 16 min. mCPP showed a retention time (RT) of 7.64 min and the internal standard eluted at 9.77 min. The mCPP peak had no overlap with other drugs of abuse. The extraction was tested >90% recovery. Furthermore, the limit of detection (LOD) was 1 mg/L and the limit of quantification (LOQ) was 5 mg/L, and the analysis proved to be linear between 0 and 150 mg/L. To confirm the identification, gas chromatography-mass spectrometry (GC/MS) (Varian Saturn 4D, Varian Medical Systems, Houten, The Netherlands) was used. The GC conditions were similar to GC-NPD, and mCPP was identified full scan (EI) with the NIST-library and
typical mass-fragment \textit{m/z} 154 and 196, and confirmed with a standard mCPP (Sigma S-014). To be able to differentiate mCPP from its isomers pCPP and oCPP, the identification of mCPP was confirmed with NMR spectroscopy in the mCPP-containing multicoloured tablets analysed in 2004.

**Statistical analysis**

The increase in the number of mCPP-containing tablets was determined using logistic regression analysis, with year as variable. Differences in doses of mCPP between tablets with and without MDMA were analysed using a one-sample \( t \)-test. Analysis of associations between reported effects and content of tablets was performed using Fischer’s exact test. A \( P \) value less than 0.05 was considered statistically significant.

**Results**

**Pharmacological content of drug samples**

Between September 2004 and December 2007, DIMS registered mCPP in 568 drug samples. mCPP was detected in 552 tablets, 7 powders, 2 capsules and 7 other samples (all parts of tablets). A total of 530 of the 552 tablets were sold as ecstasy (96.0%) (Figure 1). In total, in this period, 7947 tablets were analysed in the laboratory. Of these tablets, 7018 tablets contained MDMA (88.3%) and 552 tablets contained mCPP (6.9%). In all, 188 of the total 7947 tablets contained both MDMA and mCPP (2.4%). The number of mCPP-containing tablets increased significantly from 2004 to 2007 (\( P < 0.001 \)) (Figure 2).

**The development of mCPP on the Dutch drug market**

In the first four months after the introduction of mCPP on the Dutch drug market, from September to December 2004, DIMS registered mCPP 12 times (Figure 1). mCPP was only detected in two different types of tablets, both without a logo. All tablets were sold as ecstasy. The first type of tablet in which mCPP was identified was a beige-coloured, round-shaped tablet. However, in 2004 and in the first half of 2005, the majority of mCPP-containing tablets were off-white tablets with striking multicoloured flecks. On the street, these tablets were called ‘rainbows’, ‘harlequins’ or ‘confetti pills’.

The number of detections of drug samples containing mCPP notably increased in 2005 to 88 registered samples. Four of these samples were powders, sold as cocaine or speed, and containing between 5 and 8% of mCPP. A total of 83 samples were tablets, from which 72 tablets were sold as ecstasy and 11 were not. For most of these latter tablets, information on purchase was lacking. In the first half of 2005, three types of mCPP-containing tablets were registered, all without a logo. Most of these tablets were the so-called ‘rainbows’, easily recognised by their distinctive appearance. During the second half of 2005, the first mCPP-containing tablets with a logo appeared. The first logo was a Nike symbol, soon followed by other logos, such as V2, Versace, Rolls Royce, Lacoste and Mitsubishi. From this point on, it was no longer possible to distinguish mCPP-containing tablets from regular MDMA-containing tablets based on physical characteristics. Without the use of
laboratory analyses, the distinction could only be made by using ecstasy pill testing kits, which often make use of the Marquis test. This is a reagent test kit based on a colour reaction between a reagent liquid and a substance of abuse (Jeffrey, 2004). A typical ecstasy-like reaction will colour the liquid dark blue or black. However, pure mCPP does not produce any colour change upon contact with the reagent. The Marquis is of extremely limited value in determining the precise contents of drug samples (Winstock, et al., 2001) and is only a minor aspect in the entire drug testing procedure in the Netherlands (Spruit, 2001).

During 2005, increasing numbers of mCPP-containing tablets with different logos, colours, shapes and sizes appeared on the Dutch market of street drugs. Together with this extended variety in the outer features of mCPP-containing tablets, the content of these tablets also altered. In the first half after the introduction of mCPP, these tablets exclusively contained mCPP, but from the second half of 2005 onwards, tablets with both mCPP and MDMA started to appear on the market (Figure 2). The consequence of the addition of even a small amount of MDMA to a mCPP-tablet is a black or blue colouring in the Marquis test, similar to regular MDMA-tablets. Thus, making a distinction between both these types of tablets based on physical characteristics or on the Marquis test was no longer possible. By this time, the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) reported the detection of mCPP in all European member states (Europol – EMCDDA, 2005).

The occurrence of mCPP on the Dutch market of illegal drugs progressed throughout 2006 and 2007. DIMS registered mCPP 242 times in 2006 and 226 times in 2007, mainly in tablets sold as ecstasy. In the third quarter of 2007, almost one in every eight ecstasy tablets contained mCPP.

**Doses**

In 407 tablets, the dose of mCPP was quantified. This dose ranged from 1 to 83 mg mCPP per tablet, with an average of 27.6 ± 17.5 mg (mean ± SD). A total of 140 of these tablets also contained MDMA. The dose of mCPP in tablets containing both mCPP and MDMA was significantly lower than in tablets with only mCPP (13.3 ± 13.3 and 35.2 ± 14.5 mg, respectively; P < 0.01). In addition, in tablets containing both substances, a correlation exists between the doses of mCPP and MDMA: tablets with a low dose of mCPP do contain a higher dose of MDMA and vice versa (Figure 3).

**Subjective effects**

Until December 2007, DIMS registered 552 tablets containing mCPP since its introduction on the market in September 2004. In 79 cases, specifics were reported about the effects of the mCPP-containing tablet. In most accounts, the reported effects of these mCPP-containing tablets were negative. Most frequently reported adverse effects were nausea (54 reports) and hallucinations (18 reports) (Table 1). Other reported effects included paranoia, anxiety, dizziness, agitation, warm and cold flushes and headache. Please note that one individual can report several effects. In two cases, hospitalisation was needed after the use of mCPP-containing tablets.
From September 2004 to December 2007, DIMS registered 6830 tablets containing MDMA without mCPP. Adverse effects were reported in 60 cases. Comparing the frequency of negative effects of MDMA tablets and mCPP tablets revealed more adverse reactions to the latter type of tablets ($\chi^2 = 459.44; P < 0.01$) (Table 1). This increase in adverse effects of mCPP-containing tablets was shown for tablets containing only mCPP and for tablets with both mCPP and MDMA ($\chi^2 = 431.64$ and $169.87$, respectively; $P < 0.01$). No significant difference between tablets with only mCPP and tablets with both mCPP and MDMA was demonstrated ($\chi^2 = 1.42; P = 0.29$). In addition, frequency of the two most reported adverse effects, nausea and hallucinations, was significantly increased in all tablets containing mCPP, in tablets with only mCPP and in tablets with both mCPP and MDMA ($\chi^2 = 471.20, 420.84$ and $301.50$, respectively for nausea and $\chi^2 = 167.08, 152.32$ and $113.68$, respectively for hallucinations; $P < 0.01$).

Discussion

The percentage of mCPP-containing tablets on the Dutch market of synthetic drugs is increasing, including both tablets that contain only mCPP and tablets containing a combination of mCPP and MDMA. These mCPP tablets occur in many colours, shapes and sizes and with various logos, making it impossible to distinguish them from regular MDMA tablets. In addition, the reports of users on the effects of mCPP are predominantly negative: mCPP regularly induces severe hallucinations and nausea. All these aspects together lead to the conclusion that mCPP is an undesired addition to the ecstasy market from the user’s perspective.

Regarding the frequency of mCPP-containing drug samples detected by DIMS, it is important to bear in mind the Dutch drug testing procedure. People who go and test their drugs usually are concerned about their health and have their drugs tested before use. In addition, people can have specific motives for testing the drugs they purchased, for example, negative experiences. For this latter reason, an overestimation of the occurrence of mCPP on the ecstasy market is possible because the effects of mCPP are unwanted and people tend to have these drugs tested more frequently. Further, the identification of mCPP was only confirmed with NMR spectroscopy in the mCPP-containing multicoloured tablets (‘rainbows’) analysed in 2004. Thus, in these tablets, mCPP was differentiated from...
its isomers pCPP and oCPP. Because mass spectrometry does not distinguish mCPP from its isomers, it is possible that in other registered mCPP-containing samples these isomers are present instead of mCPP. pCPP has been reported in France and Bulgaria in drug samples similar to those registered by DIMS (Europol–EMCDDA, 2007).

The doses of mCPP detected in tablets (27.6 ± 17.5 mg, range 1–83 mg) are comparable to doses used in human psychiatric research. mCPP is extensively used as a probe of serotonin function (Kahn and Wetzler, 1991) and is administered in studies exploring the neurochemical mechanisms underlying the effects of MDMA (Tancer and Johanson, 2001; Johanson, et al., 2006). In these studies, the used oral dosages of mCPP vary between 0.25 and 0.75 mg/kg mCPP (17.5–52.5 mg mCPP for a 70-kg person). However, these are doses present in individual tablets. When several tablets are ingested, which is not an uncommon pattern in the consumption of ecstasy (Engels and Ter Bogt, 2004), these clinical doses can be exceeded. This might ultimately result in the serotonin syndrome (Klaassen, et al., 1998).

The effects reported by users reflect the effects mentioned in the literature. Side effects mentioned after the use of mCPP include anxiety, dizziness, hallucinations, nausea, warm and cold flushes, migraine and panic attacks (Gijisman, et al., 1998; Tancer and Johanson, 2001, 2003; Feuchtli, et al., 2004; Gijisman, et al., 2004). The subjective effects of mCPP resemble those of MDMA, both positive as well as negative (Tancer and Johanson, 2001, 2003). However, we found that adverse effects are more likely to occur after the use of mCPP tablets compared to MDMA tablets. Discrepancies in effects between MDMA and mCPP could be explained by differences in the effect of both drugs on the serotonin system. Whereas MDMA and mCPP both induce a release of serotonin dependent on the serotonin transporter (Rudnick and Wall, 1992; Eriksson, et al., 1999), mCPP also possesses agonist properties at some serotonin receptors (e.g., 5-HT2C) and antagonistic properties at others (e.g., 5-HT3a) (Hamik and Peroutka, 1989; Thomas, et al., 1996; Gijisman, et al., 2004). Especially, the agonistic properties of mCPP at 5-HT2 receptors can explain its hallucinogenic features because other hallucinogenic substances such as lysergic acid diethylamide exert their effects through activation of these receptors (for a review see Nichols, 2004). The activation of 5-HT3 receptors may be involved in the mCPP-induced nausea. Application of the potent 5-HT3 agonist meta-chlorophenylbiguanide (mCPBG) can cause this unfavourable effect (Higgins, et al., 1993; Kamato, et al., 1993; Wolff and Leander, 1995) and also mCPP shows relatively high affinity for the 5-HT3 receptor (Kilpatrick, et al., 1987).

In 2007, reports on cases of poisoning with mCPP (Kovalova, et al., 2008) and another piperazine, 1-benzylpiperazine (BZP) (Wood, et al., 2007), stimulated the discussion on the toxicity of piperazines (Staack, 2007). Research from New Zealand, where BZP tablets are available as ‘legal party-pills’, demonstrated that this kind of piperazines induces similar physical and psychological problems as mCPP-containing tablets, including hospital admissions (Gee, et al., 2005; Wilkins, et al., 2007). As with mCPP in the Netherlands, Gee and colleagues state that despite the fact that many users take BZP-based pills without significant adverse effects, BZP can cause unpredictable and serious toxicity in some individuals (Gee, et al., 2005). This risk of toxicity can increase when piperazines are used in combination with other drugs (Bossong, et al., 2005; Gee, et al., 2005; Staack, 2007), because the margin between the threshold dose of piperazines and the dose inducing severe adverse effects seems to be narrow (Baumann, et al., 2005). Remarkably, in contrast to the rise of mCPP on the Dutch drug market, BZP is only detected occasionally in the Netherlands.

In conclusion, the percentage of mCPP-containing tablets on the market of synthetic drugs has increased over the last few years. Because these tablets are indistinguishable from regular MDMA tablets and the majority of the reported effects of mCPP are negative, mCPP is an undesired addition to the ecstasy market from the user’s point of view.

Acknowledgements
This research was financially supported by the Dutch Ministry of Health, Welfare and Sport. The authors would like to thank F.B.A. Naber for help with statistical analysis and all prevention professionals participating in the Drug Information and Monitoring System (DIMS) for help with collecting drug samples.

References


