ELSEVIER

Drug and Alcohol Dependence 65 (2001) 97–101

DRUG and ALCOHOL DEPENDENCE

www.elsevier.com/locate/drugalcdep

Short communication

The subjective effects of MDMA and *m*CPP in moderate MDMA users

Manuel E. Tancer *, Chris-Ellyn Johanson

Substance Abuse Research Division, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI 48207, USA

Received 9 October 2000; received in revised form 27 February 2001; accepted 5 March 2001

Abstract

The present study is part of a research program designed to better understand the neurochemical mechanisms underlying the abuse liability of 3,4-methylenedioxymethamphetamine (MDMA) in humans. In these studies, MDMA will be compared to prototypical dopamine (D-amphetamine) and serotonin (*meta*-chlorophenylpiperazine, *m*CPP) releasing agents on a variety of measures related to dependence. In order to determine an acceptable dose range (safe but active) of MDMA and *m*CPP for these studies, moderate MDMA users were administered escalating doses of MDMA (75, 110 and 145 mg/70 kg) and *m*CPP (17.5, 35 and 52.5 mg/70 kg). Each participant received a single dose under controlled laboratory conditions, i.e. this was a six-group design with a separate group for each dose. There were five participants tested in each group. MDMA increased blood pressure and heart rate whereas *m*CPP had no effect on these physiological measures. MDMA produced increases in subjective effects indicative of both stimulant (increases in POMS Elation, ARCI Amphetamine, VAS High and Stimulated scale scores) and hallucinogenic effects (increases on five of the six scales of the Hallucinogenic Rating Scale). *m*CPP produced similar stimulant effects (e.g. increases on POMS Elation, VAS High and Stimulated), as well as hallucinogenic effects (four of the six scales of the Hallucinogenic Rating Scale), which has not been observed in previous studies.

Keywords: 3,4-Methylenedioxymethamphetamine; *meta*-Chlorophenylpiperazine; Hallucinogenic rating scale

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is a widely used psychoactive recreational drug with a novel pharmacology. It is a substituted amphetamine with both dopamine and serotonin releasing and reuptake inhibition properties (Iravani et al., 2000). The 'typical' street dose has been reported to be between 75 and 120 mg (Solowij et al., 1992; Mas et al., 1999), although the substances being purchased on the street vary in purity and potency and sometimes may not even contain MDMA. Several laboratory studies assessing a range of effects have been conducted with doses up to 125 mg (Vollenweider et al., 1998; Cami et al., 2000; Liechti et al., 2000).

As part of a study program designed to better understand the effects of MDMA, MDMA will be compared to prototypical dopamine (D-amphetamine) and serotonin-releasing agents on a variety of measures related to dependence. Following the removal of fenfluramine from the market, it is not clear which serotonin-releasing agent would be appropriate. *meta*-Chlorophenylpiperazine (*m*CPP) is a serotonin-releasing drug with some post-synaptic receptor agonist properties (Pettibone and Williams, 1984). While it has been widely used as a probe of serotonin systems in psychiatric populations and heavy MDMA users (Kahn and Wetzler, 1992; McCann et al., 1999), its subjective effects in moderate MDMA users have

* Corresponding author. Tel.: +1-313-5771673; fax: +1-313-5775900.

E-mail address: mtancer@med.wayne.edu (M.E. Tancer).

0376-8716/01/$ - see front matter
PII: S0376-8716(01)00146-6

not been well characterized. This is particularly important because *m*CPP appears to provoke a wide range of symptoms depending on the underlying disorder and drug history (e.g. Krystal et al., 1993; Buydens-Branchey et al., 1997).

The purpose of the present study was to determine an appropriate dose range for MDMA and *m*CPP in a population of moderate MDMA users under identical laboratory conditions in order to be able to design additional studies on the relative role of dopamine and serotonin systems in mediating the dependence-related effects of MDMA.

2. Method

Participants were recruited who were between 18 and 40 years of age, had a minimum of a high school education, and had no psychiatric or medical conditions that precluded participation. They had to have a history of stimulant drug use (at least six times) including previous MDMA use (at least three times). No candidate with a current diagnosis of a drug or alcohol dependence disorder, other than nicotine or caffeine dependence, was eligible. The study was approved by the Wayne State University Human Investigation Committee and participants were reimbursed for their time and inconvenience.

A total of 22 individuals (14 female, 8 male) participated (20 white, one bi-racial and one Arabic) with an average age of 23.6. Each participant was tested with placebo and a single dose of either MDMA [75, 110, or 145 mg/70 kg (1.1–2.1 mg/kg)] or *m*CPP [17.5, 35, and 52.5 mg/70 kg (0.25–0.75 mg/kg)] during two experimental sessions conducted at least a week apart. All MDMA groups were tested first. For safety reasons, doses for each drug were tested in ascending order with all participants in a lower dose group completing the study prior to testing the next higher doses. Five participants were assigned to each group with seven individuals participating in two groups each and one participant in three groups.

At the beginning of each experimental session, vital signs (heart rate, blood pressure) were taken and participants completed baseline mood and subjective effect rating scales. They were administered one opaque capsule containing either placebo or one of the three doses of MDMA or *m*CPP. Administration was double blind with order of administration counterbalanced. Physiological and subjective effects evaluations were obtained every hour. Six hours after drug administration, subjects completed an end of session questionnaire.

The following questionnaires were used:

Profile of mood states (POMS). This version (modified from McNair et al., 1971) consists of 72 adjectives commonly used to describe mood states and has been factor analyzed into ten scales. Participants indicate how they feel at the moment in relation to each of the adjectives.

Visual analog scales (VAS). The VAS consists of a series of seven horizontal 100-mm lines, each labeled with an adjective (stimulated, high, anxious, sedated, down, and hungry). Participants are instructed to place a mark on each line indicating how they feel at the moment from 'not at all' to 'extremely'.

Addiction research center inventory (ARCI). Martin et al. (1971) have compiled a shortened version (49 true–false items) from the 550-item ARCI that is separated into five scales.

Hallucinogen rating scale (HRS). This scale was developed and validated by Strassman et al. (1994) for measuring hallucinogenic symptoms following dimethyltryptamine administration. The HRS identifies six domains that purportedly describe hallucinogenic experiences: (a) somaesthesia; (b) affect; (c) perception; (d) cognition; (e) volition; and (f) intensity.

End of session questionnaire. At the end of each session, participants were asked to identify what drug they believed they received (stimulant, sedative, empathogen, hallucinogen, or placebo) and rate their liking of the drug's effects on a 100-mm line visual analogue scale.

Data from each group were analyzed separately. All physiological measures as well as the POMS, VAS, ARCI, and HRS were analyzed with a repeated measures two-way analysis of variance (ANOVA) with drug condition (active drug or placebo) and session time as factors. Except for the HRS, which was not administered prior to capsule ingestion, predrug baseline measures were included in the analyses. The drug identification questionnaire was not analyzed statistically whereas the liking VAS was analyzed with a one-way ANOVA with drug condition as the factor.

3. Results

On average, the participants had taken MDMA previously 14.1 times (range 3–40). None of the 22 participants dropped out of the study and no untoward effects were reported although nausea was frequently reported following the administration of *m*CPP.

All three doses of MDMA produced significant increases in systolic and diastolic blood pressure ($P < 0.04$) and 110 mg/70 kg MDMA produced significant increases in heart rate compared with placebo ($P < 0.02$). At the higher dose of MDMA there was a trend for increased heart rate ($P < 0.06$). Peak effects lasted from 1–3 h following drug administration and had returned to baseline levels by the end of the session. Maximum mean increases compared to placebo ranged from 20 to 38 mmHg for systolic blood pressure, from

15 to 19 mmHg for diastolic blood pressure, and from 18 to 25 bpm for heart rate. Increases did not appear to be dose-dependent. There were no significant effects of any of the *m*CPP doses on systolic blood pressure, diastolic blood pressure, or heart rate.

Significant subjective effects of MDMA and *m*CPP are summarized in Table 1. MDMA produced increases on several scales that indicate stimulant-like effects such as Elation (POMS), Friendly (POMS), Amphetamine (ARCI), MBG (ARCI), Stimulated (VAS) and High (VAS). Increases were also seen on both anxiety scales and the LSD of the ARCI. Increases were also seen on five of the six scales of the HRS. Most subjective effects peaked by hour two and returned to baseline levels by hour four as illustrated for the Stimulated VAS data shown in Fig. 1. Although not analyzed statistically, visual inspection of the data indicated that there was no clear dose response relationship between the magnitude of the subjective response and the dose of MDMA.

At the end of the session, all 15 subjects who received MDMA and placebo correctly identified placebo as placebo. At each dose, four of the five participants identified MDMA as an empathogen or hallucinogen with the fifth identifying it as a stimulant. On the drug liking VAS, 110 and 145 mg/70 kg had significantly higher ratings of liking ($P < 0.004$, $P < 0.008$, respectively) compared to placebo.

Like MDMA, *m*CPP produced increases relative to placebo on the elation scale of the POMS as well as arousal and confusion. On the ARCI, increases were seen on all the scales except amphetamine. Again, like MDMA, increases were seen on High and Stimulated of the VAS as well as Hungry and Sedated. The highest dose of *m*CPP produced increases on four of the scales of the HRS. Most subjective effects peaked by hour two and returned to baseline levels by hour four (Fig. 1). Although not analyzed statistically, visual inspection of the data indicated that the magnitude of the subjective responses increased with dose.

Unlike the participants in the MDMA groups, subjects in the *m*CPP groups did not consistently identify placebo or *m*CPP. At the lower dose, *m*CPP was identified by one participant as a hallucinogen, one as a stimulant and three as placebo. Placebo was identified by four of the five as placebo. At the intermediate dose, *m*CPP was identified by one participant as a hallucinogen, one as a stimulant, two as an empathogen, and one

Table 1
Significant subjective effects of MDMA and *m*CPP compared with placebo[a]

	75 mg/70 kg MDMA	110 mg/70 kg MDMA	145 mg/70 kg MDMA	17.5 mg/70 kg *m*CPP	35 mg/70 kg *m*CPP	52.5 mg/70 kg *m*CPP
POMS						
Anxiety	–	D*	D			
Arousal					D*T	
Confusion	–	–	D, D*T			
Elation	D*T #	–	–			D*T #
Friendly	D	–	–			
Vigor					D*T	D
ARCI						
Amphetamine	D	–	D			
BG					D	D*T
LSD	D*T	D, D*T	D*T			D
MBG	–	–	D			D*T
PCAG					D*T	
VAS						
Anxiety	–	–	D			
High	D, D*T	D, D*T	D, D*T		D*T	D*T
Hungry				D*T		
Sedated						D*T
Stimulated	D, D*T	D*T	D, D*T		D*T	D
HRS						
Intensity	D, D*T	–	D, D*T			D*T
Soma	D, D*T	D*T	D, D*T			D*T
Affect	–	–	D			D*T
Perception	D, D*T	D	D, D*T			D*T
Cognition	D, D*T	–	D, D*T			

[a] D, indicates a significant ($P < 0.05$) main drug effect with scores for the active drug condition higher than the scores for placebo. D*T, indicates a significant ($P < 0.05$) drug by time interaction with scores for the active drug condition higher than the scores for placebo with the exception of PCAG for 35 mg/70 kg *m*CPP where drug decreased the score relative to placebo. #, $P < 0.055$.

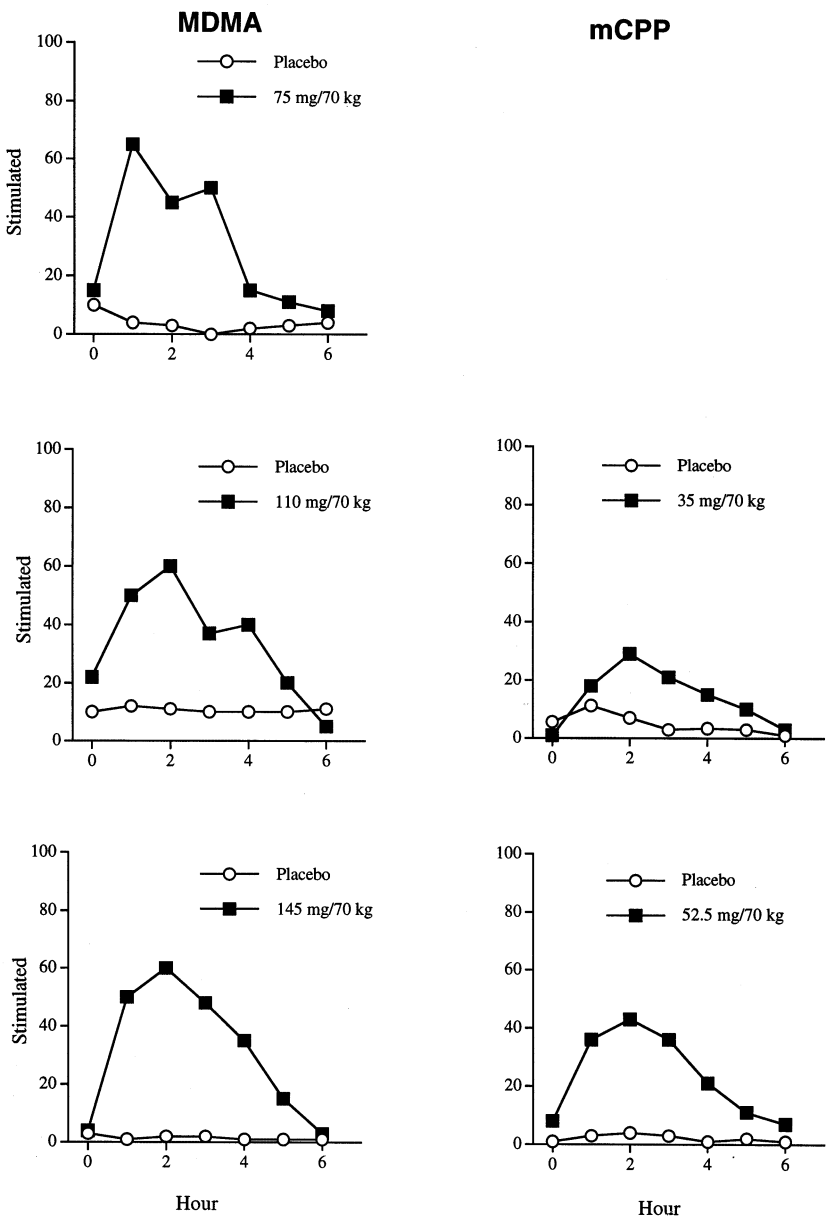

Fig. 1. The effects of 75, 110, 145 mg/70 kg MDMA (left panels) and 35 and 52.5 mg/70 kg *m*CPP (right panels) compared to placebo (open symbols) on the stimulated visual analog scale as a function of time since oral administration. Different groups of subjects (five per group) received placebo and each dose.

as placebo. Placebo in this group was identified by two as a sedative, one as a stimulant, and two as placebo. At the higher dose, *m*CPP was identified by one as a sedative, two as a stimulant, one as an empathogen, and one as a placebo. Placebo in this group was identified by one as a sedative, one as a stimulant, and three as a placebo. The drug liking ratings for *m*CPP did not differ statistically from placebo at any of the three doses.

4. Discussion

This study demonstrates that both MDMA and *m*CPP can be safely administered to moderate MDMA users in a laboratory situation at doses that produce robust subjective effects. MDMA, but not *m*CPP, had significant effects on both heart rate and blood pressure similar to those reported by Mas et al. (1999), but these were well tolerated and short in duration. MDMA had subjective effects that are similar to those seen with amphetamine although these effects peaked earlier and were shorter in duration (Chait et al., 1986). These results were qualitatively similar to those reported by others (e.g. Cami et al., 2000; Liechti et al., 2000). Interestingly, the effects did not appear dose-dependent even though a dose higher (145 mg/70 kg) than that used in previous studies was tested. *m*CPP exhibited some euphoric responses, a pattern that has been reported in heavy MDMA users

(average use 196 times; McCann et al., 1999) as well as cocaine addicts (Buydens-Branchey et al., 1997). In addition, *m*CPP was reported as having stimulant, dysphoric, anxiogenic, and sedative effects. Both MDMA and *m*CPP produced increases on many of the scales of the HRS indicating hallucinogenic properties, which was not expected for *m*CPP. MDMA was also identified as a hallucinogen/empathogen but this was not true for *m*CPP. However, for both drugs the magnitude of the responses was not as great as reported by Strassman et al. (1994) with dimethyltryptamine. In summary, even as doses higher than previously reported, MDMA appears safe to use under laboratory conditions and produces both stimulant and hallucinogenic effects. *m*CPP is devoid of physiological effects in the dose range tested but nevertheless produces robust changes in subjective effects, including those that are hallucinogenic.

Acknowledgements

This research was supported by Joe Young Funds awarded to the Department of Psychiatry and Behavioral Neurosciences by the State of Michigan.

References

Buydens-Branchey, L., Branchey, M., Fergeson, P., Hudson, J., McKernin, C., 1997. The meta-chlorophenylpiperazine challenge test in cocaine addicts: hormonal and psychological responses. Biol. Psychiatry 41, 1071–1086.

Cami, J., Farre, M., Mas, M., Roset, P.N., Poudevida, S., Mas, A., San, L., de la Torre, R., 2000. Human pharmacology of 3,4-methylenediosxymethamphetamine (''ecstasy''): psychomotor performance and subjective effects. J. Clin. Psychopharmacol. 20, 455–466.

Chait, L.D., Uhlenhuth, E.H., Johanson, C.E., 1986. The discriminative stimulus and subjective effects of D-amphetamine, phenmetrazine and fenfluramine in humans. Psychopharmacology 89, 301–306.

Iravani, M.M., Asari, D., Patel, J., Wieczorek, W.J., Kruk, Z.L., 2000. Direct effects of 3,4-methylenedioxymethamphetamine (MDMA) on serotonin or dopamine release and uptake in the caudate putamen, nucleus accumbens, substantia pars reticularlat, and the dorsal raphe nucleus slices. Synapse 36, 275–285.

Kahn, R.S., Wetzler, S., 1992. m-Chlorophenylpiperazine as a probe of serotonin function. Biol. Psychiatry 30, 1139–1166.

Krystal, J.H., Siebyl, J.P., Price, L.H., Woods, S.W., Heninger, G.R., Aghajanian, G.K., Charney, D.S., 1993. m-Chlorophenylpiperazine effects in neuroleptic-free schizophrenic patients. Evidence implicating serotonergic systems in the positive symptoms of schizophrenia. Arch. Gen. Psychiatry 50, 624–635.

Liechti, M.E., Saur, M.R., Gamma, A., Hell, D., Vollenweider, F.X., 2000. Psychological and physiological effects of MDMA (''Ecstasy'') after pretreatment with the 5-HT(2) antagonist ketanserin in healthy humans. Neuropsychopharmacology 23, 396–404.

Martin, W.R., Sloan, J.W., Sapira, J.D., Jasinski, D.R., 1971. Physiologic, subjective and behavioral effects of amphetamine, ephedrine, phemetrazine, and methylphenidate in man. Clin. Pharmacol. Ther. 12, 245–258.

Mas, M., Farre, M., De La Torre, R., Roset, P.N., Ortuno, J., Segura, J., Cami, J., 1999. Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. J. Pharmacol. Exp. Ther. 290, 136–145.

McCann, U.D., Eligulashvili, V., Mertl, M., Murphy, D.L., Ricaurte, G.A., 1999. Altered neuroendocrine and behavioral responses to m-chlorophenylpiperazine in 3,4-methylenedioxymethamphetamine (MDMA) users. Psychopharmacology 147, 56–65.

McNair, D.M., Lorr, M., Droppelman, L.F., 1971. Manual for the Profile of Mood States. Educational and Industrial Testing Service, San Diego.

Pettibone, D.J., Williams, M., 1984. Serotonin-releasing effects of substituted piperazines in vitro. Biochem. Pharamcol. 33, 1525–1531.

Solowij, N., Hall, W., Lee, N., 1992. Recreational MDMA use in Sydney: a profile of ''Ecstasy'' users and their experiences with the drug. Br. J. Addict. 87, 1161–1172.

Strassman, R.J., Qualls, C.R., Uhlenhuth, E.H., Kellner, R.K., 1994. Dose response study of N,N-dimethyltryptamine in humans. Arch. Gen. Psychiatry 51, 98–108.

Vollenweider, F.X., Gamma, A., Liechti, M., Huber, T., 1998. Psychological and cardiovascular effects and short-term sequelae of MDMA (''Ecstasy'') in MDMA-naive healthy volunteers. Neuropsychopharmacology 19, 241–251.