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Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations

Charles S. Grob [a*], Russell E. Poland [a], Linda Chang [b], Thomas Ernst [b c]

[a] *Department of Psychiatry, Bldg. D-6 (Box 498), Harbor-UCLA Medical Center, 1000 W. Carson Street, Torrance, CA 90509, USA*
[b] *Department of Neurology, Harbor-UCLA Medical Center, Torrance, CA 90509, USA*
[c] *Department of Radiology, Harbor-UCLA Medical Center, Torrance, CA 90509, USA*

Abstract

3,4-Methylenedioxymethamphetamine (MDMA) is a phenethylamine with potent effects on serotonergic neurotransmission which has been the object of controversy over its potential as a therapeutic adjunct versus its possible risks for causing neurotoxic injury. This paper discusses the background, methodology and preliminary findings of the first FDA approved Phase I study prospectively evaluating the effects of MDMA administration in humans. Six subjects with prior experience with MDMA were administered two different dosages of MDMA and an inactive placebo utilizing a randomized, double-blind methodologic design. Dosages from 0.25 to 1.0 mg/kg, p.o., were administered. All subjects tolerated the procedures without any overt evidence of physical discomfort or psychological distress. MDMA produced a modest increase in heart rate and blood pressure. The threshold dose for the stimulation of ACTH and prolactin appeared to be between 0.5 and 0.75 mg/kg, with the two higher doses clearly stimulating both ACTH and prolactin. Methodology for assessing MDMA's effects on serotonergic neurotransmission is discussed.

Keywords: 3,4-Methylenedioxymethamphetamine (MDMA); Neurotoxicity; Serotonin; Hallucinogen; Neuroendocrine challenge; Fenfluramine; Single photon emission computerized tomography (SPECT); Spectroscopy

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is a phenethylamine with structural similarities to both mescaline and amphetamine. It was first synthesized in Germany before the First World War, but largely ignored by the scientific research community until the mid 1970s. Since then MDMA has acquired popularity as a potential treatment for psychiatric disorders, achieved notoriety as a dangerous drug of abuse and aroused concern as a putative neurotoxin. Human research designed to study this controversial compound has been limited owing to its placement as a Schedule 1 drug in 1985. This study is the first FDA approved protocol designed to prospectively evaluate the effects of MDMA in humans.

Modern interest in MDMA was catalyzed by Shulgin and Nichols in 1978 [28], who reported that the substance induced "an easily controlled altered state of consciousness with emotional and sensual overtones", and suggested that MDMA might be useful as an adjunct to psychotherapy. Its apparent facility in inducing heightened states of empathic rapport has been identified as a particularly pertinent element of MDMA's suggested therapeutic mechanism of action [6,7]. Although reports of successful response of conditions often refractory to conventional treatment were encouraging, no well-controlled prospective research design was implemented to test claims of alleged therapeutic efficacy. Following MDMA's scheduling in the mid 1980s, this unconventional form of treatment no longer had legal sanction, although its clandestine use apparently continued [2].

Although various estimates have been given on the extent of illicit MDMA use in the United States and western Europe, the exact prevalence remains unknown. Saunders [27] has stated that "millions" of (young) people in England have taken MDMA. In 1992, a Harris Opinion Poll [10] for the BBC Reportage program in England presented data that 31% of people between the ages of 16 and 25 reported taking the drug, most often at 'dance clubs'. In a survey of school children across the whole of England, 4.5% of 14 year olds and, in another survey, 6.0% of 14 and 15 year olds had taken

* Corresponding author. Fax: (1) (310) 3287217.
E-mail: GROB@AFP76.HUMC.EDU.

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MDMA [27]. In the United States, a recent NIDA report [21] indicates that 2.0% of all US college students had taken MDMA in the previous 12 months. In 1987, Peroutka [22] reported that 39% of undergraduate students interviewed at Stanford University had taken MDMA at least once, while a 1990 Tulane University survey revealed that 24.3% of over 1200 students questioned had experimented with the drug [3].

In 1985, scheduling hearings on MDMA were conducted by the DEA. Although the DEA's administrative law judge at that time expressed his view that there was sufficient evidence for safe utilization under medical supervision and recommended Schedule III status [32], he was subsequently overruled by the DEA Director who placed MDMA in Schedule I [14]. A factor given at that time for this decision was the timely report that a related substance, MDA (3,4-methylenedioxyamphetamine), caused 'neurotoxic' changes in the brains of rats [25]. Subsequently, considerable efforts have been expended to demonstrate similar findings in animals treated with MDMA [18].

Preclinical investigations of MDMA-induced neurotoxicity have aroused considerable concern that humans who take the drug will experience deleterious functional consequences attributed to toxic brain damage [23]. Investigations of human users, however, have not provided convincing evidence of severe adverse sequelae. In fact, studies purporting to demonstrate signs of 'neurotoxicity' in humans [13,24] have subsequently been questioned due to methodological concerns [8], including subject inclusion criteria which might have biased the results indicative of central serotonergic (5-HT) dysfunction [9]. Although reports of evident severe adverse acute effects have recently been published, particularly in the British literature [11,17], the numbers of such case reports have remained surprisingly small given the burgeoning degree of use. Other investigators have reported that individuals with moderate histories of MDMA use who utilized careful preparation and adequate safeguards appeared to have tolerated their experiences without apparent deleterious functional sequelae [15,31]. A more thorough evaluation of long-term MDMA users has found an association between lower levels of CSF 5-HIAA (the major metabolite of serotonin) and diminished aggression and impulsivity [16], and long-term effects on Stage II sleep and sleeptime [1]. All such investigations, however, have been hampered by retrospective methodologies, necessitated by legal constraints. The study presented here is the first FDA-sanctioned prospective design implemented to advance the inquiry into MDMA's effects on human central nervous system function.

2. Design

This Phase I study of the effects of MDMA in normal volunteers with prior experience with MDMA has received approval from the US FDA, DEA, California Research Advisory Panel and Harbor-UCLA Research and Education Institute IRB. All prospective subjects are carefully screened to exclude individuals with histories of major psychiatric disorders (including schizophrenia, major affective disorder, panic disorder and obsessive compulsive disorder), seizure disorders and histories of alcohol or substance abuse within the past year. All subjects must be free of psychoactive medication and illicit drug use for 1 month prior to the study and during the study.

Assessment prior to the actual MDMA administration sessions includes a neuropsychological testing battery designed to measure memory function as well as frontal lobe skills, fenfluramine (and placebo) challenge tests (with serial assays of prolactin, cortisol and ACTH), sleep electroencephalography for assessment of 5-HT function, ^{133}Xenon calibrated ^{99m}Tc-HMPAO SPECT (single photon emission computerized tomography) scans (co-registered with MRI) [19] to assess regional cerebral blood flow and proton spectroscopy (^{1}H-MRS) [26] for analysis of brain neurochemistry [4,12]. The pre-MDMA administration battery is repeated 2 weeks following the final MDMA session.

All subjects participate in 3 experimental randomized, double-blind drug sessions, receiving different dosages of (±)-MDMA (on a mg/kg basis) on two occasions and an inactive placebo on the third. Each experimental drug session begins at 12.00 h and lasts for 8 h, and is performed in our NIH supported General Clinical Research Center. During experimental drug sessions, blood is drawn every 30 min, 2 h prior to (4 samples) and 6 h following (12 samples) MDMA administration, from an indwelling intravenous catheter. MDMA pharmacokinetics and neuroendocrine response are assessed. ACTH is measured by a two-site IRMA (Nichols Institute) and prolactin is measured by a standard radioimmunoassay. For each hormone, all samples from each subject are measured in the same assay. Maximum intra- and inter-assay variability is 8.9%.

Measurements also are made each 30 min of oral temperature, heart rate and blood pressure. Mood and anxiety are periodically assessed using the POMS-SR and STAI, respectively. An Altered States Graphic Profile (Metzner, personal communication) examining hedonic and arousal continuums is marked every 15 min and the Hallucinogen Rating Scale [29] is administered at the conclusion of the session.

3. Results

As of November, 1994, 6 subjects had completed the MDMA administration protocol. Dosages administered ranged from 0.25 to 1.0 mg/kg, p.o. Owing to space limitations, full review of results and data analyses is

not feasible. Some of our finding are highlighted below: All 6 subjects who completed the protocol tolerated the MDMA administration well without evident difficulty. One additional subject who had been recruited into the study dropped out after one experimental drug session complaining of anxiety during the session. After the subject had withdrawn from the protocol, the blind was broken, revealing that he had been administered an inactive placebo during his only session.

As shown in Table 1, vital signs were not significantly affected by MDMA administration, although heart rate and blood pressure were modestly increased by the drug.

Table 1
Mean (±S.E.M.) changes (Δ) of temperature, heart rate, systolic blood pressure, and diastolic blood pressure in response to placebo and various doses of MDMA in 6 subjects

	Placebo	MDMA (mg/kg, p.o.)			
		0.25	0.50	0.75	1.00
Δ Temperature (°F)	−0.19±0.41	−0.31±0.72	0.49±0.45	0.41±0.22	−0.20±0.44
Δ Heart rate (beats/min)	2.0±1.7	−2.4±3.9	2.6±1.5	4.0±5.8	8.8±8.5
Δ Systolic blood pressure (mm Hg)	5.2±3.1	3.5±0.05	7.0±0.54	8.5±1.5	19.5±7.9
Δ Diastolic blood pressure (mm Hg)	2.0±1.7	−2.4±3.9	2.6±1.5	4.0±5.8	8.8±8.5

Each subject received placebo and two doses of MDMA. During each session, a single delta (Δ) value was derived for each measure. The Δ response for each subject was determined by subtracting the average of the 4 baseline prechallenge values from the average of the 12 postchallenge values during each session.

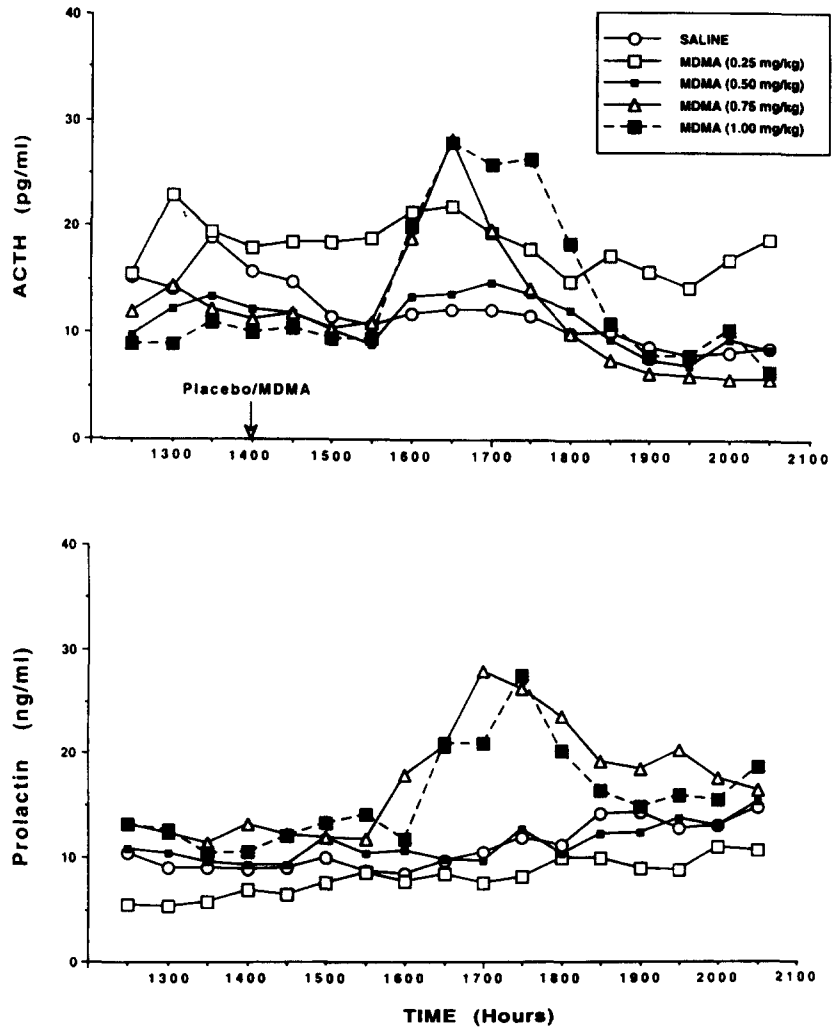

Fig. 1. Mean ACTH and prolactin responses to placebo and MDMA. Blood samples were obtained at 30-min intervals prior to and following placebo and MDMA administration at 14.00 h.

The threshold dose of MDMA for stimulation of ACTH and prolactin appears to be between 0.50 and 0.75 mg/kg. ACTH and prolactin were increased significantly ($P \leq 0.05$) by MDMA (0.75 mg/kg) ($n=4$), with a similar trend observed for the 1.0 mg/kg dose ($n=2$) (Fig. 1 and Table 2). These responses are consistent with activation of serotonergic neurotransmission and preclinical data in rodents [20,30]. We have found that both ACTH and prolactin are stimulated in rodents by comparable doses of MDMA (Poland and Grob, unpublished).

SPECT studies of 5 subjects at baseline revealed a strong positive correlation between regional cerebral blood flow (rCBF) and frequency of MDMA exposure.

As shown in Fig. 2, ^{1}H-MRS performed in the occipital lobe revealed a 25% decrease in the choline (CHO) peak in one 38-year-old female subject who had previously used MDMA 10 times (the last time 7 weeks prior to study), as compared to an age-, gender- and race-matched normal control. No difference in the *N*-acetyl-aspartate (NA) peak (a neuronal marker) was observed between the control and MDMA subject. Two weeks following the second dose of MDMA (0.5 mg/kg), total creatine + phosphocreatine (CR) was found to be increased 20%, CHO remained low, but NA remained essentially unchanged.

Indices of positive psychological states during MDMA administration increased with dose (0.25–1.0 mg/kg).

Neuropsychological status remained stable over time.

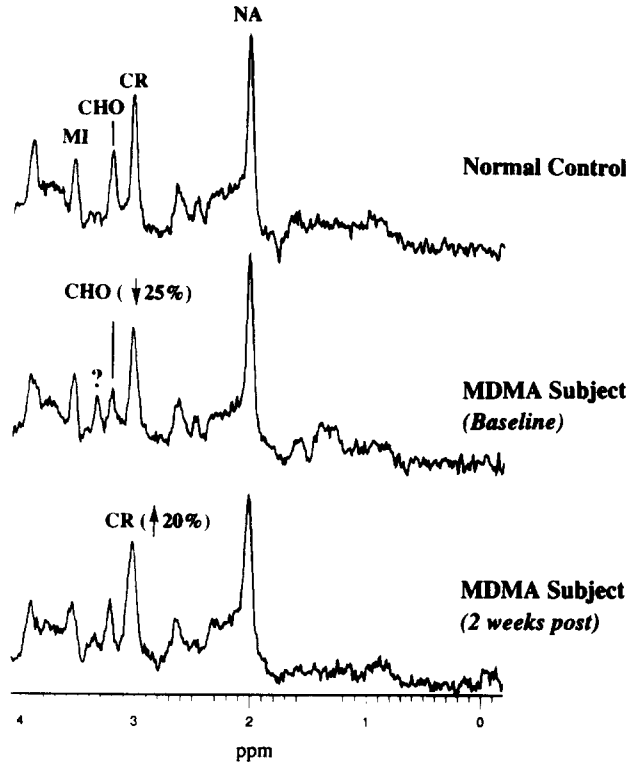

Fig. 2. Proton MR spectra of an MDMA user before (middle spectrum) and 2 weeks after (bottom spectrum) administration of the second of two doses (separated by 2 weeks) of MDMA (0.25 and 0.50 mg/kg, p.o.). The top spectrum is from a normal age-, sex- and race-matched control subject. Spectra are normalized so that peak areas can be directly compared. The spectra were acquired from the mid-occipital region, using a STEAM sequence with TE = 30 ms and TR = 2 s [5].

4. Conclusions

Preliminary data have been presented on the first sanctioned prospective investigation of the psychobiologic effects of MDMA in humans. Although our findings of the first 6 subjects studied are intriguing, definitive conclusions must await further controlled inquiry of the effects of higher dose administration. The study design calls for additional subjects to receive MDMA in the 1.0–1.75 mg/kg range, which then will be followed by the study of 1.75–2.5 mg/kg dosages.

Past studies have suffered from lack of prospective design, thus impeding adequate elucidation of not only MDMA's inherent risk for causing harm, but also its potential for therapeutic application. An emotional and acrimonious political atmosphere has clouded careful and impartial examination of MDMA's full range of effects. Precedent now has been established for conducting sanctioned investigation in human subjects under safe and controlled condition. Technical advances will allow for more careful monitoring and assessment of the psychobiologic effects of MDMA in humans. Critical questions concerning MDMA's putative risks to public health versus the potential benefits of new treatment

Table 2
Mean (±S.E.M.) changes of ACTH and prolactin response to placebo and various doses of MDMA in 6 subjects

	Placebo	MDMA (mg/kg, p.o.)			
		0.25	0.50	0.75	1.00
Δ ACTH (pg/ml)	−5.6±3.3	−2.0±1.4	−1.1±1.0	0.1±1.6	5.0±1.9
Δ Prolactin (ng/ml)	−0.6±1.6	2.9±2.1	1.8±0.84	6.3±4.6	5.5±2.4

Each subject received placebo and two doses of MDMA. During each session, a single delta (Δ) value was derived for each hormone. The Δ response was determined by subtracting the average of the 4 baseline prechallenge hormone values from the average of the 12 postchallenge hormone values.

modalities await to be answered. Prospective research designs utilizing the controlled administration of MDMA to humans offer the best hope of revealing its true, inherent, risk/benefit ratio.

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