ELSEVIER

International Journal of Drug Policy 9 (1998) 119–124

THE INTERNATIONAL JOURNAL OF DRUG POLICY
OFFICIAL JOURNAL OF THE INTERNATIONAL HARM REDUCTION ASSOCIATION

MDMA research: preliminary investigations with human subjects

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Abstract

This report will discuss recent developments in MDMA research. Between May 1994 and November 1995, a US FDA approved Phase 1 investigation of 3,4-methylenedioxymethamphetamine (MDMA) in normal volunteers was conducted at the Harbor-UCLA Medical Center. A double blind, placebo-controlled model, utilizing a range of dosages up to 2.5 mg/kg, was implemented. A variety of medical, biochemical and psychobiologic parameters were incorporated as assessment measures. Results of this pilot investigation will be reviewed.

Keywords: 3,4-Methylenedioxymethamphetamine; Placebo; Medical parameters

1. Introduction

The phenethylamine 3,4-methylenedioxymethamphetamine (MDMA) has structural similarities to both mescaline and methamphetamine. MDMA has been at the center of heated controversy during the last 15 years over its suggested role as a public health threat, most notably its purported capacity to cause neurotoxic brain damage versus its potential to facilitate successful psychiatric treatments, particularly in patients refractory to conventional therapies. First synthesized in 1891 by German chemists (Haber, 1891) and patented by Merck on 16 May, 1914, MDMA investigations were terminated with the outbreak of World War I. It fell into obscurity for the next 40 years, when it was selected as part of the US Military Intelligence MKULTRA project investigating various psychoactive substances for their potential as 'brain washing' agents. Basic animal toxicity studies were initiated, however, human experimentation was never conducted because of a fatal reaction induced in a military 'volunteer' who reportedly died following administration of an excessive amount (several times the recognized dosage range) of 3,4-methylenedioxyamphetamine (MDA), an analogue of MDMA (Lee and Shlain, 1985). The effects of MDMAs in humans were not systematically examined until the early 1970s, when the eminent pharmacological researcher, Alexander Shulgin, resynthesized the compound and administered it

0955-3959/98/$19.00
PII S0955-3959(98)00008-5

to himself and several colleagues. Intrigued by what he considered to be a unique array of effects, Shulgin introduced MDMA to a number of mental health professionals to explore in the psychotherapy setting (Shulgin and Nichols, 1978; Shulgin and Shulgin, 1991).

During the late 1970s and early 1980s, an estimated several hundred accredited psychotherapists in the US made use of MDMA (at that time still a legal compound) administration as an integral component to their treatments. Utilizing the old and discarded models from the 1950s and 1960s used in treatments with psychedelic drugs, heavy emphasis was given to (a) preparation of the: patient; (b) intent; (c) ritual structure; (d) set; (e) setting; and (f) integration of the experience. Unlike the classical psychedelics (e.g. LSD, psilocybin, mescaline), MDMA was reported to induce a several hour long, pleasant, easily controlled experience, marked by lowered defensive anxiety, elevated mood, enhanced introspection and improved capacity to articulate feeling states (Adamson and Metzner, 1988). Furthermore, MDMA, in contrast to the classical psychedelics, was reputed to not cause perceptual disturbances, impair orientation or disrupt ego identity (Liester et al., 1992). Accordingly, some experts enthusiastically contended that MDMA held great promise as a superior adjunct to psychotherapy, both in its ease of administration as well as its much lower societal profile, than the controversial psychedelics (Grinspoon and Bakalar, 1986; Greer and Tolbert, 1990).

In the mid-1980s MDMA became the focus of intense scrutiny and controversy in the media, not only because of its association to previously discredited models of psychedelic psychotherapy but because of its increasing recreational use by young people. Alarmed by this sudden surge of popularity of a previously unknown substance, the US Drug Enforcement Agency called for emergency scheduling of MDMA. Although the DEAs own administrative lawjudge subsequently recommended Schedule 3 status, having concluded that MDMA could be administered safely under medical supervision (Young, 1986), the DEAs final decision was to place MDMA in the most restrictive category, Schedule 1 (Lawn, 1986). Justification for classifying MDMA as a Schedule 1 substance was attributed to expressed concern from certain neuroscientists that MDMA might have potential injurious effect on the central nervous systems of users as well as alarm over its growing use, under the name of 'Ecstasy', by young people. Over the past decade, substantial pre-clinical research activity has been devoted to demonstrating that MDMA induces alterations in brain neurons containing the neurotransmitter, serotonin (McKenna and Peroutka, 1990). Although short-term degeneration of serotonergic axonal projections has been clearly demonstrated, investigators have failed to establish that such changes lead to deleterious functional consequences in the laboratory animals studied. Similarly, the extrapolation of these animal studies to the concept of MDMA induced 'neurotoxicity' in humans has remained controversial and awaits further elaboration (Grob et al., 1990, 1992; Grob and Poland, 1997).

The use of MDMA, particularly by young people, has continued to grow. Although its early use was almost exclusively in the US, by the late 1980s MDMA had spread to Europe. Achieving its peak popularity in Great Britain, where an estimated 500000 are reported to take MDMA every weekend (Sylvester, 1995) The use of 'Ecstasy' has spread throughout the continent, with its apparent greatest density of use in Germany, Switzerland, Holland and Spain. Ironically, its application as a modality of psychotherapy is virtually unknown in Europe, where its use is predominantly within the context of all-night marathon dances called 'raves' (Saunders, 1995). As its popularity has continued to rise in recent years, associated medical risks have received greater attention. Perhaps associated with the declining purity and reliability of what is an illicitly manufactured and marketed product which has not been subjected to any degree of quality control (Bost, 1988; Buchanan and Brown, 1988; Wolff et al., 1996), increasing reports of adverse outcomes have been published in the medical and psychiatric literatures. These have included a series of deaths attributed to MDMA induced malignant hyperthermia within the context of all night marathon dances without sufficient access to

necessary rehydration (Henry et al., 1992). Additional reported adverse events have included cerebrovascular accidents (Manchanda and Connolly, 1993), cardiovascular collapse (Dowling et al., 1987), liver damage (Dykhuizen et al., 1995) and mental status deterioration (McGuire et al., 1994). It is noteworthy, however, that given the extraordinary numbers of individuals who have taken MDMA (estimated on the order of millions worldwide) and the adverse circumstances under which it is often consumed (a product of ill defined purity, not infrequently ingested along with alcohol and other drugs, inevitably taken by some individuals with serious underlying medical and psychiatric illness who may be taking prescribed medication and often in the context of arduous exercise without adequate fluid replacement), there have not been more instances of deleterious outcome reported.

Because of the enormous public health implications of millions of young people taking a potent psychoactive substance about which substantive questions have yet to be answered, as well as the lingering potential that this class of drug may represent a viable treatment alternative to individuals suffering from conditions refractory to conventional therapies, direct examination of MDMA's effects in humans would appear to be indicated.

2. Methodology

In May, 1994, the first US FDA approved research investigation examining the effects of MDMA administered to human subjects was initiated at Harbor-UCLA Medical Center in Torrance, California. Collaborators for this Phase 1 research project on the effects of MDMA in humans, in addition to the author, included Russell E. Poland, Linda Chang and Thomas Ernst. Over an 18-month period, a total of 18 normal volunteer subjects were administered MDMA on the Harbor-UCLA Medical Center Clinical Research Unit utilizing a placebo-controlled, double blind research methodology. All subjects, as per stipulation of the FDA, had had prior first hand experience with MDMA. Ages ranged from 20 to 62 years, with 12 being male and six female. Prior experience with MDMA ranged from one experience to over 800.

Prior to enrollment in the MDMA administration study, each prospective subject received a physical examination, blood chemistry evaluation and a structured psychiatric interview. Individuals with histories or evidence of serious medical (e.g. cardiovascular, hematologic, endocrine and neurological disorders) or psychiatric (e.g. schizophrenia, major affective disorder, panic disorder, obsessive-compulsive disorder) were excluded from the study. Prospective subjects who met diagnostic criteria for alcohol or substance abuse within the previous year or who reported use of cocaine, amphetamines or opioids within the prior 2 years, were denied entry into the study. All individuals accepted for participation as subjects in this research investigation were instructed to not consume any psychoactive substance, inclusive of alcohol, marijuana and hallucinogens, as well as MDMA outside of the context of the study, until their full participation in this Phase 1 MDMA evaluation, including follow-up assessments, had been concluded.

Additional baseline evaluation before MDMA administration included neuropsychological testing, MR (magnetic resonance) spectroscopy and SPECT (single photon emission computerized tomography) brain scans. Subjects received repeat neuropsychological, MR spectroscopy and SPECT scan evaluations, 2 weeks following the final experimental drug session. Each subject participated in three experimental drug sessions on the Harbor-UCLA Clinical Research Unit, spaced 2 weeks apart. On two of these occasions subjects received different dosages of MDMA (ranging from 0.25 to 2.5 mg/kg) and on one occasion an inactive placebo. A double blind methodology was utilized, along with randomization of the ordering of the experimental drug sessions. Subjects remained resting in bed and were encouraged to drink fluids throughout the experimental drug session. Administration of the experimental drug was standardized for 14:00 h for each of the sessions. Blood draws from an indwelling intravenous catheter were initiated at 12:30 h and continued at 30-min intervals until 20:00 h. Blood

samples were later assayed for cortisol, ACTH and prolactin, to determine neuroendocrine response to MDMA, as well as for pharmacokinetics, to measure persistence of MDMA and its metabolites over time. Vital signs (including temperature, heart rate and blood pressure) were measured every 30 min. Instruments designed to assess subjective psychological status, including the profile of mood states (POMS), state-trait anxiety inventory (STAI) and the altered states graphic profile (ASGP) were filled out by the subjects at 30-min intervals.

3. Results

Preliminary data analyses of results of this Phase 1 research investigation of the effects of MDMA in humans have previously been published (Grob et al., 1996) and will briefly be updated and summarized. Neuroendocrine challenge assays of cortisol, ACTH and prolactin secretion have revealed robust increases in hormonal secretion beginning approximately 1-h following MDMA administration, peaking at the 1.5-h point for ACTH and prolactin and at the 2.5-h point for cortisol. Secretion returned to baseline and placebo levels by the 5-h point for ACTH and prolactin but still remained modestly elevated for cortisol by the final blood draw at the 6-h point. Preliminary pharmacokinetic analyses indicated maintenance of virtually peak levels of MDMA and its primary metabolite MDA by the 6-h point.

Vital sign measurements demonstrated modest though significant changes, particularly for subjects administered medium dose (1.0–1.75 mg/kg) and high dose (2.0–2.5 mg/kg) range MDMA. Mild temperature elevations were observed with mid and high dose MDMA administration, peaking at 1°F at about the 3.5-h point. The heart rate was noted to increase steadily between the 1 to 2-h points and gradually decline thereafter. Evaluation of blood pressure response was complicated by two subjects who sustained significant blood pressure elevations in response to MDMA administration. One subject, a 28-year-old man who subsequently revealed that he had taken a friend's anti-asthmatic medication the morning of the experimental drug session after experiencing an 'allergic' response to a cat who was in the house he had slept in the night before arriving at the hospital (although he neglected to inform research personnel that he had taken this medication until after the experimental drug administration), sustained a significant elevation of systolic and diastolic blood pressure from a normal baseline of 120/80 to a peak of 200/100 at the 1-h point. Blood pressure with this subject remained elevated for only 1/2 h and then rapidly returned to baseline. A second subject, a 62-year-old man, with baseline blood pressure of 130/85, sustained a rapid elevation to a peak of 220/120 at the 1-h point which he maintained for approximately 1.5 h and then gradually returned to baseline. The subject reported no discomfort or adverse symptoms during this experience. All other subjects experienced only modest elevations of blood pressure. Instruments designed to measure subjective psychological states proved to be of mixed value. Both the POMS and the STAI revealed only the lack of negative symptomatology during the experimental drug sessions. The ASGP on the other hand, proved to be a valuable measure of progressive alterations of subjective states of consciousness over time. Each of the two dimensions of experience examined, the hedonic continuum and the arousal continuum, revealed significant changes in the positive direction with both medium dose and high dose ranges.

Prior to the first experimental drug administration session and 2 weeks following the last, subjects received neuropsychological evaluation, MR spectroscopy and SPECT brain scans. A matched control group of individuals who had never taken MDMA were also subjected to similar studies. Baseline neuropsychological evaluations revealed no significant differences between subjects with histories of MDMA use and non MDMA using controls. Follow-up neuropsychological testing 2 weeks following the final experimental drug session demonstrated no significant changes from baseline assessment. Both MR spectroscopy as well as SPECT scans did reveal intriguing changes, however, it is important to preface such findings with the fact that only a relatively small

number of subjects were studied in these pilot investigations. Preliminary findings, however, indicated possible alterations of brain neurochemistry and blood perfusion, particularly in the visual cortex of the occipital lobe. Preliminary analyses of MR spectroscopy data showed elevations of brain creatine in direct proportion to the cumulative dosage of MDMA administered, whereas SPECT findings indicated a trend towards chronic elevation of blood perfusion in long-term MDMA users (when compared to normal controls) in the face of sub-acute decline (compared to baseline) when evaluated 2 weeks following the last experimental drug session. The implications of these preliminary findings to the ongoing debate over MDMA's effects on central nervous system function remain unclear and await further elucidation.

4. Conclusions

Although first synthesized over 100 years ago and at the center of more recent controversy over its suggested application as an important psychiatric treatment modality versus its purported capacity to induce neurotoxic brain damage, MDMA has failed to receive adequate formal and prospective evaluation of its effects in humans until recently. Given its degree of use by increasing numbers of youth, careful and controlled scrutiny of its range of effects would appear timely, if not long overdue. Accordingly, the first approved Phase 1 research investigation of MDMA administration in humans was conducted at the Harbor-UCLA Medical Center between May 1994 and November 1995.

A variety of neuropsychiatric and medical parameters were subjected to intensive scrutiny. Particularly interesting findings relevant to MDMA's recent widespread use as a 'dance' drug included mild temperature elevations in subjects resting comfortably in bed who were encouraged to drink fluids and significant blood pressure elevations in 2/18 subjects with apparent idiosyncratic vulnerabilities to cardiovascular perturbations.

Given the ongoing debate over MDMA's alleged capacity to cause 'neurotoxicity' and thus impair brain function, considerable attention was given to evaluating the drug's effect on central nervous system function. Comprehensive neuropsychological testing revealed no baseline evidence of deleterious effects on cognition, memory or concentration in individuals with histories of MDMA use or prospectively in subjects administered the drug. Sophisticated brain scanning assessments posed more challenging questions. Although revealing of intriguing changes in both baseline (chronic) as well as subacute measures, indicating that there may indeed be both short and long term modulation of parameters of brain perfusion, chemistry and function, the numbers of subjects studied were too small for these findings to be appreciated as anything more than preliminary and suggestive.

The issue of MDMA poses a challenge to the neuropsychiatric professions. MDMA is a potent psychoactive compound, used illicitly by millions, feared as a 'neurotoxic' agent, yet lauded as a powerful facilitator of positive treatment outcome. Formal, controlled research until recently has been restricted and neglected. For the feared risks and suggested benefits of MDMA to be fully understood, further rigorous, methodological investigations will need to be undertaken. Hopefully, the Harbor-UCLA MDMA Phase 1 study will serve as a model to other research groups that approved and well-controlled investigations can be successfully pursued. It will only be then, when collaborative, multi-center research studies have been accomplished, that it will definitively have been established what MDMA's true capacity is to induce harm versus its innate potential to facilitate healing.

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