Pharmacology of MDMA in Humans

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ABSTRACT: MDMA given at recreational doses (range tested 50 to 150 mg) to healthy volunteers, produced mydriasis and marked increases in systolic and diastolic blood pressure, heart rate, and pupillary diameter. MDMA induced changes on oral temperature. The time course of this observation was biphasic, as a slight decrease at 1 h and a slight increase at 2 and 4 h were observed. MDMA induced a slight dose-dependent impairment on psychomotor performance. MDMA produced a marked rise in plasma cortisol and prolactin concentrations. The elimination half-life of MDMA was about 8–9 h. Drug concentrations increased, and a parallel increase in physiologic and hormonal measures was observed. Both peak concentrations and peak effects were obtained between 1 and 2 h and decreased to baseline values 4–6 h after drug administration.

INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA) is an amphetamine derivative that seems to exert mixed stimulant and hallucinogenic effects. In contrast with amphetamines and other stimulants, which act mainly through noradrenergic and dopaminergic mechanisms, MDMA possesses serotonergic activity. This could confer to this drug its distinct actions, sharing some that are typical of stimulant drugs and others that are from hallucinogens.

MDMA administration in humans evidences salient cardiovascular and neurologic sympathomimetic effects. Increased blood pressure and pulse rate and mucocutaneous vasoconstriction are commonly observed, as also are diaforesis, mydriasis, dry mouth, jaw clenching, trismus, and bruxism. In addition, MDMA seems to have some deleterious effects on psychomotor performance, associated with a subjective feeling of confusion that could be related to its serotonergic-induced hallucinogenic effects. Additionally, MDMA disposition in the body seems to follow a nonlinear pharmacokinetics that could have implications in cases of acute intoxication.[1,2] Metabolism of MDMA involves *N*-demethylation to 3,4-methylenedioxyamphetamine (MDA). The parent compound and MDA are further *O*-demethylenated to 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. Both HHMA and HHA are subsequently *O*-methylated mainly to 4-hydroxy-3-methoxy-methamphetamine (HMMA) and 4-hydroxy-3-methoxy-amphetamine (HMA). These four metabolites, particularly HMMA and HMA, are known to be ex-

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creted in the urine as conjugated glucuronide or sulfate metabolites, but data on plasma concentrations and urinary quantitative recovery of these metabolites and their potential relationship with the administered dose are scarce.[3]

The pharmacology of MDMA in humans has been recently described in two reports where experimental data related to psychologic effects, psychomotor performance, subjective effects, neuroendocrine-induced changes, and pharmacokinetics obtained in healthy volunteers administered with single oral MDMA doses (75 mg and 125 mg) were presented.[4,5] Some of the effects observed were in a dose-dependent pattern. In the present paper, experimental data from a new clinical trial administering an intermediate dose of 100 mg of MDMA to healthy volunteers are presented.[6] Results obtained with the three MDMA doses in the clinical trials and some additional doses assayed in pilot studies of these trials are compared.[7] New pharmacokinetic data concerning MDMA metabolites are presented.

SUBJECTS AND METHODS

Subjects. Twenty-seven healthy male recreational users of MDMA participated in different randomized, double-blind, placebo-controlled, crossover clinical trials. They had ingested MDMA between 5 and 50 times in their lives (25 occasions on the average), were moderate or social alcohol consumers, and all of them had previous experience with cannabis, cocaine, and methamphetamine consumption. None had a history of abuse or drug dependence according to DSM-IV criteria (except for nicotine dependence), or any medical or psychiatric adverse reaction after MDMA consumption.

All volunteers gave their written informed consent and were economically compensated for inconveniences caused by their participation in the study. The studies were conducted in accordance with the Declaration of Helsinki, approved by the Ethical Committee of our institution, and authorized by the Spanish Ministry of Health (nos. 95/297 and 98/112).

d,l-MDMA was administered in oral single doses. In different studies, two volunteers were administered with 50 mg, 10 with 75 mg, 13 with 100 mg, 8 with 125 mg, and two with 150 mg. In one study the same 8 subjects had 75 mg and 125 mg doses; the subject-dose count totaled up to 35 (27 + 8) among 27 volunteers. In all studies, data on physiologic parameters, psychomotor performance, subjective effects, neuroendocrine changes, and pharmacokinetics were collected.

Physiologic parameters. Noninvasive heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and oral temperature were recorded using a Dinamap™ 8100-T vital signs monitor (Critikon, Tampa, FL). Pupillary diameter was recorded with a Haab pupil gauge. For safety reasons, ECG was continuously monitored during the entire session using a Dinamap™ Plus vital signs monitor (Critikon).

Psychomotor performance. The psychomotor performance battery included the simple reaction time, the DSST, and the Maddox-wing device. The simple reaction time was assessed using the Vienna Reaction Unit (PC/Vienna System, Schufried, Austria). Results were expressed in milliseconds as the mean of the response time to 20 stimuli (total reaction time), which can be split into decision time and motor time. A computerized version of DSST was used. Scores were based on the number of cor-

rect patterns keyed in 90 s (correct responses). The Maddox-wing device measures in diopters the balance of extraocular muscles and quantifies exophoria, as an indicator of extraocular musculature relax, and esophoria. Details of all these procedures have been previously described.[5]

Samples. An indwelling intravenous catheter was inserted in a peripheral vein, and a 0.9% sodium chloride solution was infused at a rate of 20 ml/h. Blood samples (6 ml, heparinized tubes) were obtained for analysis of MDMA and its main metabolites (MDA, HMMA, HMA) at 0 and at 15, 30, 45, 60, and 90 min, and at 2, 3, 4, 6, 8, 10, and 24 h after drug administration. In addition, a 4-ml sample for hormone analysis (cortisol and prolactin) was drawn and collected in nonheparinized tubes at 0 and at 30, 60, and 90 min, and at 2, 3, 4, and 6 h after drug administration. Samples were centrifuged at 3000 rpm for 10 min and at 4°C. Plasma and serum were removed and frozen at −20°C until analysis.

Assays. For MDMA and metabolites analysis, plasma aliquots of 1 ml were allowed to thaw at room temperature and processed. Samples were analyzed by gas chromatography coupled to a nitrogen phosphorous detector (GC/NPD) or to a mass selective detector (GC/MS).

The extraction procedure for GC/MS analysis of MDMA and its metabolites was performed using a method previously reported, using [$^2H_5$]MDMA, [$^2H_5$]MDA, and pholedrine as internal standards.[8]

Gas chromatography-mass spectrometry analysis was performed in a Hewlett Packard 6890 gas chromatograph coupled to a model 5973 quadrapole mass spectrometer (Palo Alto, CA). The samples were injected in splitless mode into a 12 m × 0.2 mm I.D., 0.33 μm film thickness 5% phenylmethylsilicone column (Ultra 2-Hewlett Packard). The oven temperature was initially maintained at 70°C during 2 min and programmed to 160°C at 30°C per min, then to 170°C at 5ºC per min, to 200°C at 15°C, and finally to 280°C at 30°C per min. The injector and the interface were operated at 280°C. Helium was used as carrier gas at a flow rate of 1.2 ml/min. The mass spectrometer was operated by electron impact ionization and in the selected ion monitoring acquisition mode. Ions m/z 154 for MDMA, HMMA, and pholedrine; m/z 162 for MDA; m/z 260 for HMA; m/z 158 for [$^2H_5$]MDMA; and m/z 167 for [$^2H_5$]MDA were selected for quantification. Calibration curves were linear over the 25–400 ng/ml concentration range for MDMA and HMMA and over the 2.5–40 ng/ml concentration range for MDA and HMA. Limits of quantification were 5.7 ng/ml for MDMA, 1.0 ng/ml for MDA, 2.9 ng/ml for HMMA, and 0.5 ng/ml for HMA. Interday precision (expressed as coefficient of variation for specific added target concentrations) and accuracy (expressed as percentage error of concentration found as compared with target added concentrations) were lower than 3.3 and 4.4% for MDMA, 6.7 and 4.9% for MDA, 3.8 and 8.4% for HMMA, and 11.1 and 1.5% for HMA. Intraday precision and accuracy were lower than 4.4 and 2.5% for MDMA, 3.4 and 0.2% for MDA, 5.0 and 6.1% for HMMA, and 10.1 and 0.8% for HMA.

Serum cortisol concentrations were determined by fluorescence polarization immunoassay (FPIA) (Abbott Laboratories, Chicago, IL) according to the manufacturer's instructions.

Serum prolactin concentrations were determined by a microparticle enzyme immunoassay (MEIA) (Abbott Laboratories) using an IMx^R instrument and following the manufacturer's instructions.

Pharmacokinetics and statistical analysis. With regard to plasma concentrations of MDMA and its metabolites, the following parameters were determined: peak concentration (C_{max}), time taken to reach peak concentration (t_{max}), and area under the concentration-time curve from 0 to 24 h ($AUC_{0–24}$) and from 0 to infinite (AUC_{total}). Pharmacokinetic parameters of MDMA and metabolites including absorption and elimination half-life were calculated using a computer program (PKCALC).[9] Results from all variables were transformed to differences from baseline, and, when sample size allowed for it, repeated measures ANOVA with drug condition and time as factors, and post-hoc Tukey's test were used for comparison between active conditions and their corresponding placebo. Differences associated with *p* values lower than 0.05 were considered to be statistically significant.

RESULTS

Sympathomimetic effects. Effects of MDMA on physiologic measures are shown in TABLE 1 and FIGURE 1 (systolic blood pressure, upper trace). All doses, except 50 mg, induced increases of systolic and diastolic blood pressure, pulse rate, and pupillary diameter. The magnitude of effects and their duration were related to the dose administered, and at doses of 75 mg and higher some subjects met criteria for hypertension and sinusal tachycardia. Changes in oral temperature had a biphasic time course, as MDMA induced a slight decrease at 1 h and a slight increase at 2 and 4 h.

Psychomotor performance. MDMA induced a slight dose-dependent impairment of DSST. Total reaction time marginally increased, mainly due to increases in decision time, but did not reach statistically significant differences. At all doses, except 50 mg, MDMA induced esophoria in the Maddox wing. Results are presented in TABLE 2 and FIGURE 1 (Maddox wing, lower trace).

Hormones. Neuroendocrine effects after the administration of MDMA (75, 100, and 125 mg) and placebo are shown in FIGURE 2. Plasma cortisol concentrations were significantly higher after the administration of MDMA as compared with placebo. The peak differences in the plasma cortisol concentration between MDMA 125 and placebo were 17.3 µg/dl, between MDMA 100 and placebo 19.6 µg/dl, and between MDMA 75 and placebo 13.4 µg/dl. Cortisol concentrations peaked at 2 h after MDMA administration.

Plasma prolactin concentrations were significantly higher after the use of MDMA 125 and 100 than after the administration of placebo, and MDMA 75. Peak differences between MDMA 125 and placebo were 17.4 ng/ml; between MDMA 100 and placebo 22.1 ng/ml; and between MDMA 100 and MDMA 75 15.7 ng/ml. Plasma prolactin concentrations peaked at 2 h after MDMA administration.

MDMA and metabolites pharmacokinetics. Time course of plasma concentrations of MDMA, MDA, HMMA, and HMA are presented in FIGURE 3. Experimental (C_{max}, $t_{max,}$ and $AUC_{0–24}$) and calculated pharmacokinetic parameters for MDMA and metabolites at the dose of 100 mg are presented in TABLE 3. With regard to MDMA, t_{max} was observed at 2 h. Plasma levels declined following a monoexponential model. Mean elimination half-life was 9 h after the 100 mg dose.

Plasma concentrations of MDA appeared slowly after MDMA administration. Peak concentrations (C_{max}) of 13.1 ng/ml for the MDMA 100 mg dose were reached

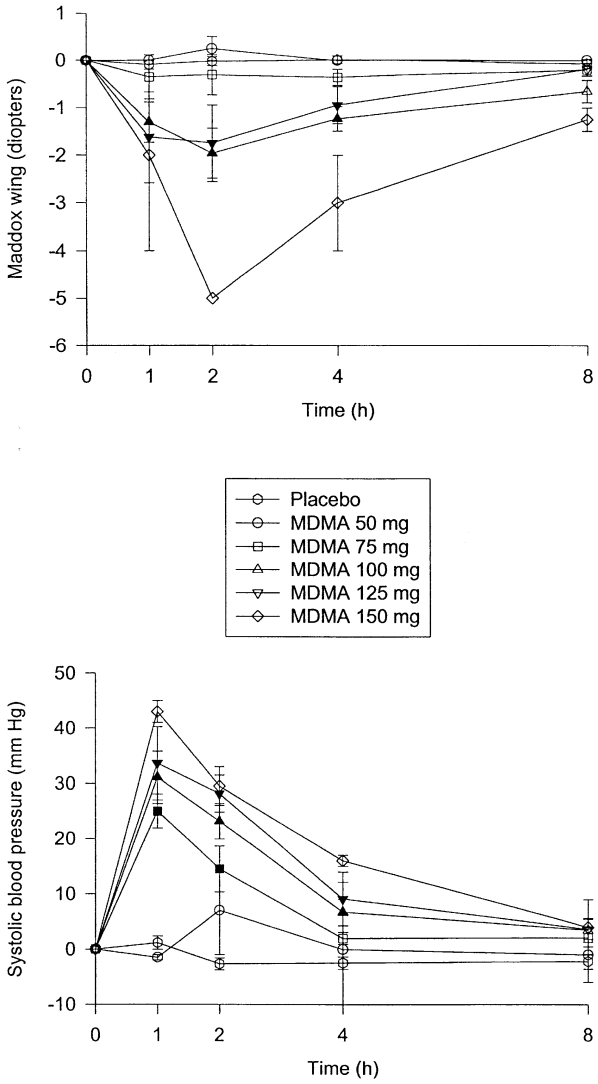

FIGURE 1. *Upper trace*: MDMA effects on systolic blood pressure, expressed as mean ± SE of differences from baseline. *Lower trace*: MDMA effects on Maddox wing, expressed as mean ± SE of differences from baseline. Results were obtained from 27 male healthy recreational MDMA users: 50 mg ($n = 2$); 75 mg ($n = 10$); 100 mg ($n = 13$); 125 mg ($n = 8$); 150 mg ($n = 2$); (eight subjects took 75 and 125 mg). Filled symbols mean significant differences compared to corresponding placebo.

TABLE 1. MDMA effects on physiologic measures, expressed as mean ± SE of differences from baseline

Measure	MDMA Dose (mg)	Time (h) 1	2	4	8
Systolic blood pressure (mm Hg)	50	−2 ± 1	7 ± 8	0 ± 14	−1 ± 5
	75	25 ± 3**	15 ± 4**	2 ± 1	2 ± 2
	100	31 ± 5**	23 ± 2**	7 ± 2**	3 ± 2
	125	34 ± 7**	28 ± 3**	9 ± 3*	4 ± 2
	150	43 ± 2	30 ± 4	16 ± 1	4 ± 5
Diastolic blood pressure (mm Hg)	50	1 ± 5	−2 ± 5	−8 ± 6	−8 ± 5
	75	12 ± 3**	6 ± 2*	−1 ± 1	−3 ± 2
	100	14 ± 3**	11 ± 2**	2 ± 3*	−5 ± 2
	125	12 ± 4**	15 ± 2**	1 ± 2	−7 ± 2
	150	20 ± 2	10 ± 8	5 ± 3	−9 ± 1
Pulse rate (b/min)	50	7 ± 2	−1 ± 4	2 ± 7	10 ± 3
	75	21 ± 4**	17 ± 4**	7 ± 2**	10 ± 2
	100	29 ± 4**	24 ± 4**	10 ± 2**	12 ± 2**
	125	24 ± 5**	20 ± 4**	14 ± 4**	15 ± 3*
	150	32 ± 1	29 ± 3	27 ± 8	27 ± 5
Oral temperature (ºC)	50	0.55 ± 0.2	0.65 ± 0.6	0.70 ± 0.3	0.95 ± 0.1
	75	−0.25 ± 0.1**	0.36 ± 0.1**	0.33 ± 0.1**	0.22 ± 0.1
	100	−0.27 ± 0.1**	0.33 ± 0.2**	0.40 ± 0.1**	0.35 ± 0.1
	125	−0.16 ± 0.2**	0.34 ± 0.1*	0.41 ± 0.1**	0.23 ± 0.1
	150	−0.05 ± 0.5	0.65 ± 0.6	0.05 ± 0.1	0.45 ± 0.3
Pupillary diameter (mm)	50	N.A.	N.A.	N.A.	N.A.
	75	2.5 ± 0.3**	2.6 ± 0.3**	1.9 ± 0.2**	1.1 ± 0.2**
	100	2.9 ± 0.2**	3.7 ± 0.2**	2.1 ± 0.2**	0.8 ± 0.2**
	125	2.6 ± 0.5**	3.0 ± 0.3**	2.3 ± 0.2**	0.8 ± 0.3**
	150	4.3 ± 0.8	3.8 ± 0.8	3.3 ± 0.3	0.8 ± 0.3

NOTE: Results were obtained from 27 male healthy recreational MDMA users: 50 mg ($n = 2$); 75 mg ($n = 10$); 100 mg ($n = 13$); 125 mg ($n = 8$); 150 mg ($n = 2$); (eight subjects took 75 and 125 mg). Pupillary diameter was not measured in subjects on 50 mg MDMA (N.A.). Symbols: $^{*}p < 0.05$; $^{**}p < 0.01$, compared to corresponding placebo.

at 5–7 h after administration. In reference to MDA pharmacokinetic, the MDA formation rate constant has been estimated for the 100 mg MDMA dose of being about 0.63 h^{-1}. Elimination half-life of MDA was around 25 h.

HMMA and HMA displayed plasma concentrations very similar to those corresponding to their metabolic precursors MDMA and MDA, respectively.

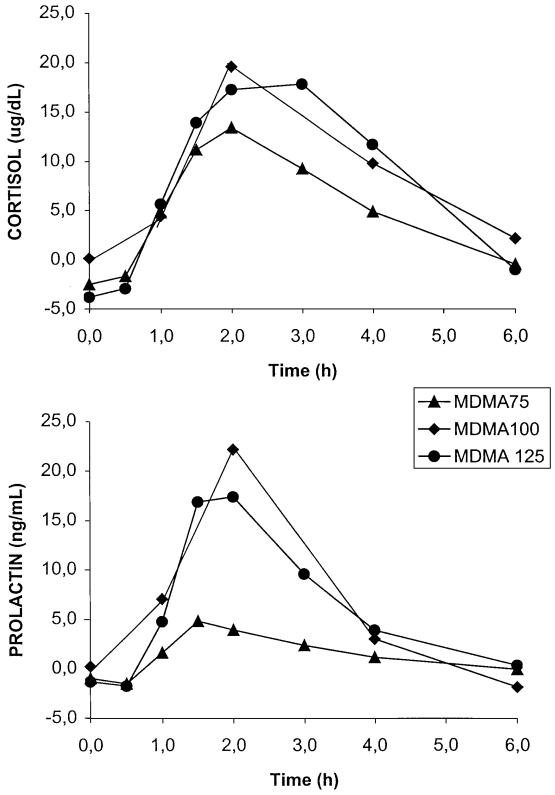

FIGURE 2. MDMA effects on cortisol (*upper trace*) and prolactin (*lower trace*) plasma concentration, expressed as mean ± SE of differences from baseline. Results were obtained from 27 male healthy recreational MDMA users: 50 mg (n = 2); 75 mg (n = 10); 100 mg (n = 13); 125 mg (n = 8); 150 mg (n = 2); (eight subjects took 75 and 125 mg).

DISCUSSION

Sympathomimetic activity. MDMA administration at doses between 75 and 150 mg produced marked increases in blood pressure and heart rate. These findings agree with previous studies,[10,11] taking into account the dose differences between studies: approximately 15–75 mg and 120 mg, respectively. A related substance, 3,4-methylenedioxyethylamphetamine (MDEA, approximately 100–140 mg), produced a similar response pattern.[12,13] MDMA also induced a pronounced mydriasis that lasted longer than the cardiovascular effects. Hypertension, tachycardia, and mydriasis are common features of MDMA intoxication, and are attributable to its symphatomimetic properties.

In our studies, a slight decrease in oral temperature is observed at 1 h, which could be related to the important mucocutaneous vasoconstriction observed during

TABLE 2. MDMA effects on psychomotor performance measures, expressed as mean ± SE of differences from baseline

Measure	MDMA Dose (mg)	Time (h) 1	2	4	8
Correct DSST (number)	50	−3.0 ± 2.0	0.5 ± 1.5	−1.0 ± 1.0	0.0 ± 1.0
	75	−1.7 ± 1.1	0.6 ± 0.5	1.0 ± 0.6	1.4 ± 0.7
	100	−1.0 ± 1.3	−1.2 ± 1.1	0.5 ± 1.0	0.5 ± 0.7
	125	−2.9 ± 0.7*	−1.0 ± 1.0	0.4 ± 0.6	0.8 ± 0.4
	150	−22.5 ± 6.5	−10.0 ± 2.0	−2.5 ± 0.5	−3.5 ± 0.5
Total reaction time (ms)	50	−16 ± 9	−12 ± 4	−1 ± 27	−17 ± 8
	75	17 ± 11	10 ± 11	15 ± 13	3 ± 8
	100	18 ± 10	10 ± 10	13 ± 8	4 ± 11
	125	28 ± 13	22 ± 11	10 ± 8	13 ± 11
	150	45 ± 23	96 ± 57	15 ± 24	−18 ± 4
Decision reaction time (ms)	50	−7 ± 18	−6 ± 4	−3 ± 2	−3 ± 7
	75	16 ± 10	9 ± 10	8 ± 11	−2 ± 8
	100	18 ± 8	14 ± 8	6 ± 4	5 ± 6
	125	26 ± 13	21 ± 14	8 ± 9	3 ± 9
	150	40 ± 11	107 ± 59	30 ± 18	3 ± 2
Motor reaction time (ms)	50	−9 ± 26	−6 ± 1	2 ± 26	−15 ± 2
	75	1 ± 5	1 ± 5	7 ± 7	5 ± 5
	100	−1 ± 5	3 ± 6	7 ± 7	−2 ± 6
	125	2 ± 8	1 ± 7	2 ± 5	10 ± 6
	150	6 ± 12	31 ± 39	−15 ± 6	−20 ± 2
Maddox wing (diopters)	50	0.0 ± 0.0	0.3 ± 0.3	0.0 ± 0.0	0.0 ± 0.0
	75	−0.4 ± 0.5	−0.3 ± 0.4	−0.4 ± 0.2	−0.2 ± 0.1
	100	−1.3 ± 0.4**	−2.0 ± 0.5**	−1.2 ± 0.3**	−0.7 ± 0.2
	125	−1.6 ± 1.0**	−1.8 ± 0.8**	−0.9 ± 0.4*	−0.2 ± 0.1
	150	−2.0 ± 2.0	−5.0 ± 0.0	−3.0 ± 1.0	−1.3 ± 0.3

NOTE: Results were obtained from 27 male healthy recreational MDMA users: 50 mg ($n = 2$); 75 mg ($n = 10$); 100 mg ($n = 13$); 125 mg ($n = 8$); 150 mg ($n = 2$); (eight subjects took 75 and 125 mg). Symbols: $^{*}p < 0.05$); $^{**}p < 0.01$, compared to corresponding placebo.

the earliest phase of MDMA effects manifestation. Furthermore, for the first time a significant slight increase in oral temperature was evidenced at 2 and 4 h after MDMA administration. Such changes in body temperature have been associated with neurotoxicity of amphetamines. Nevertheless, when reviewing data on oral temperature in healthy volunteers administered with MDMA in a laboratory

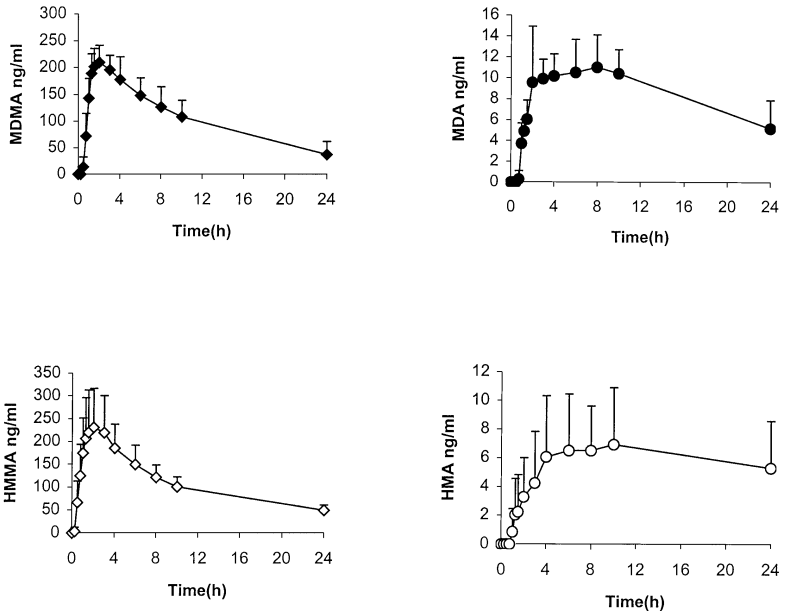

FIGURE 3. Concentration time course for MDMA and its metabolites (dose MDMA, 100 mg), expressed as mean ± SE ($n = 8$).

setting,[4,10,11] only marginal increases in body temperature have been observed as compared with reported hyperthermia in cases of acute intoxication.

Psychomotor performance. In our study a slight decrease in psychomotor performance results was evidenced. These results are in contrast with the mild enhancement of performance usually observed with amphetamine. Moreover, volunteers experienced subjective feelings of confusion, mental slowing, and impaired attention. Similar feelings were reported in a previous study, along with a slight but not significant psychomotor impairment in the Stroop task.[11] The mechanism of this impairment is unknown, but could be related to a mild hallucinogenic-like effect induced by the serotonergic activity of MDMA. The discrepancy between the results on Stroop tests, simple reaction time and DSST could be attributable to the fact that DSST requires more complex cognitive involvement and attention. This explanation is consistent with the finding that MDMA impaired total reaction time mainly because of an increase in decision time.

MDMA induced esophoria in the Maddox wing, a finding opposed to the effect of sedatives, which generally produce a clear-cut exophoria caused by extraocular musculature relaxation. In contrast, cocaine did not produce changes in this test.[14] A possible explanation could be related to an alteration of accommodation due to mydriasis or sympathomimetic activation.

Hormones. In relation to the neuroendocrine effects, MDMA produced significant increases in plasma cortisol and prolactin concentrations. The lack of global dif-

TABLE 3. Pharmacokinetic parameters for MDMA and metabolites (MDMA 100 mg administered to 8 subjects)

	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0\text{-}24}$ (ng/ml.h^{-1})	AUC_{total} [a] (ng/ml.h^{-1})	k_a [b] (h^{-1})	k_e (h^{-1})	$t_{½a}$ [c] (h)	$t_{½}$ (h)
MDMA								
Mean	222.50	2.3	2431.38	3053.15	2.70	0.081	0.34	8.96
± SD	26.06	1.1	766.52	1115.85	1.53	0.018	0.22	2.27
MDA								
Mean	13.13	6.7	191.78		0.63	0.035	1.31	24.89
± SD	4.47	2.6	58.34		0.33	0.017	0.55	14.53
HMMA								
Mean	236.66	2.3	2592.22	3351.60	2.31	0.064	0.34	11.25
± SD	87.12	0.9	668.80	748.78	0.91	0.014	0.15	2.86
HMA								
Mean	7.50	8.2	132.00		0.40	0.023	1.83	37.37
± SD	4.00	1.67	86.82		0.12	0.024	0.58	17.93

ABBREVIATIONS: C_{max} = peak plasma concentration; t_{max} = time of peak plasma concentration; $AUC_{0–24}$ = area under the curve from 0 to 24 h; AUC_{total} = area under the curve from 0 to infinite; k_a = absorption constant; k_e = elimination constant; $t_{½a}$ = absorption half-life; $t_{½}$ = elimination half-life.

[a]Not calculated for MDA.

[b]Formation constant rate in the case of MDA, HMMA or HMA.

[c]Formation half-life in the case of MDA, HMMA, or HMA.

ferences between MDMA doses of 100 and 125 mg, even if different sets of subjects are compared, suggest that a plateau in the rise of cortisol and prolactin concentrations is reached. Intermediate responses as demonstrated with the MDMA 75 mg dose are possible. These results are consistent with previous studies where increases in ACTH and prolactin concentrations were reported after use of 0.75–1 mg/kg of MDMA.[10] Although cortisol increases are consistent with activation of serotonergic neurotransmission, dopaminergic and noradrenergic mechanisms may also be involved. Prolactin secretion is mainly mediated by dopaminergic and serotonergic systems. In humans, MDEA also increases cortisol and prolactin plasma concentrations.[12,13]

MDMA and metabolites pharmacokinetics. To our knowledge, this is the first complete description of the pharmacokinetics of MDMA and its metabolites after its administration to a considerable number of subjects in the range of doses used for recreational purposes. Previous reports described mainly MDMA and MDA pharmacokinetic parameters. The t_{max} was attained at 2 h, a result similar to that reported by Helmlin *et al.*[15] and Verebey *et al.,*[16] although it was reached at 4 h in the study of Henry *et al.*[17] Peak concentrations, taking into account the proportions between doses, are also in agreement with the mentioned previous findings. The elimination half-life of MDMA 100 mg was about 8–9 h, similar to that reported after 50, 75, and 125 mg. These values are lower than those reported for methamphetamine (10–12 h) or amphetamine (12–15 h).

A possible nonlinear pharmacokinetics of MDMA has been suggested when considering together the present results and those of the pilot studies and controlled ones at doses of 75 and 125 mg. After the administration of 150 mg to two volunteers, a disproportional increase in MDMA plasma concentrations was observed.[1,2] Several mechanisms have been proposed to explain the nonlinear kinetics of MDMA and include either a simple saturation of drug metabolism or the formation of a complex between a metabolite and the enzyme.[18] The MDMA nonlinear kinetics should be confirmed in studies with a design specifically addressing this issue.

MDA, formed by *N*-demethylation of MDMA, appears to be a minor metabolite, representing 8–9% of the concentrations of MDMA (AUC comparisons) for all the doses tested. This finding is further supported by the fact that MDA urinary recovery is about 1% of the dose administered, while for methamphetamine the *N*-demethylated product (amphetamine) is about 10%.

HMMA is the main metabolite of MDMA either in plasma or in urine. Plasma concentrations observed are quite similar to those corresponding to MDMA. Interestingly, this metabolite is close to the detection limit when analyzed in its free form, being necessary an enzymatic hydrolysis of the plasma samples for its determination. Urinary recovery of this metabolite at a dose of 100 mg is about 13–14% of the dose in 24 h, while MDMA recovery is 24%. Higher recoveries are observed with lower MDMA doses while the contrary is observed at higher doses. These findings are consistent with the nonlinear pharmackinetics phenomenon described for MDMA. Body clearance of HMMA is a little longer than that described for MDMA, as the estimated elimination half-life is about 11 h.

HMA is a minor MDMA metabolite; $AUC_{0-24\,h}$ is similar to the one observed for MDA, its metabolic precursor. The same observation is applicable to MDMA and HMMA. Urinary recovery of this metabolite is very low, about 1.5% of the dose in 24 h. Its elimination half-life presented in TABLE 3 is probably overestimated, and addtional samples should be collected after 24 h for a better estimate.

In the analytical conditions applied for the determination of MDMA and its metabolites, intermediate metabolic products dihydroxymethamphetamine (HHMA) and dihydroxyamphetamine (HHA) are not detected in plasma and only at very low concentrations in urine. Both metabolic products are very unstable and can be either rapidly further metabolized by the catechol-methyltransferase, observing in biological fluids only the final product HMMA or HMA; or analytical conditions should be improved for a better determination. In any case, the analysis of these inetrmediate metabolites deserves further research in the light of the complexity of MDMA metabolism.

The time course of blood concentrations of MDMA and its pharmacological effects rise and fall with a similar profile. Drug concentrations increased, and parallel increases in physiologic and hormonal measures were observed. Both peak concentrations and peak effects were obtained between 1 and 2 h and decreased to return to baseline values 4–6 h after drug administration.

In summary, MDMA given at recreational doses produced mydriasis and marked increases in blood pressure, heart rate, and plasma cortisol and prolactin concentrations. Its elimination half-life was about 8–9 h. According to these findings obtained in the laboratory setting, MDMA consumption in crowded conditions, high ambient temperature, and physical activity ("rave parties") may be associated with a potential life-threatening increase in the toxicity of the drug.

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