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ORIGINAL INVESTIGATION

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Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics

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Abstract *Rationale:* 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is increasingly used by young people for its euphoric and empathic effects. MDMA presents non-linear pharmacokinetics, probably by inhibition of cytochrome P450 isoform 2D6. Users are known to often take more than one dose per session. This practice could have serious implications for the toxicity of MDMA. *Objective:* To evaluate the pharmacological effects and pharmacokinetics of MDMA following the administration of two repeated doses of MDMA (24 h apart). *Methods:* A randomised, double-blind, cross-over, placebo controlled trial was conducted in nine healthy male subjects. Variables included physiological, psychomotor performance, subjective effects, endocrine response and pharmacokinetics. MDMA 100 mg or placebo was administered in two successive doses separated by an interval of 24 h. *Results:* MDMA produced the prototypical effects of the drug. Following a second dose, plasma concentrations of MDMA increased (AUC 77% and C_{max} 29%) in comparison with the first. The increase is greater than those expected by simple accumulation and indicates metabolic inhibition. The pharmacological effects after the second dose were slightly higher than those observed after the first in the majority of variables including blood pressure, heart rate, most subjective effects and cortisol concentrations. The effects were similar in the case of pupil diameter, esophoria and prolactin. *Conclusions:* Pharmacological effects after the second administration were higher than those following the first but lower than expected. A disproportionate increase in plasma concentrations in MDMA and MDA was observed most likely due to metabolic inhibition. This inhibition lasts at least 24 h. Further experiments need to be conducted to evaluate its duration.

Keywords MDMA · Ecstasy · Repeated dose · Metabolic inhibition · Pharmacological effects · CYP2D6 · Humans

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Introduction

MDMA (3,4-methylenedioxymethamphetamine, ecstasy) is a ring-substituted amphetamine, structurally similar to methamphetamine and mescaline. It acts as an indirect serotonin agonist, inducing serotonin release from neuronal endings and inhibiting its re-uptake. In addition, MDMA is a potent releaser of dopamine and norepinephrine (White et al. 1996).

MDMA given at single recreational doses in experimental settings has produced marked increases in blood pressure, heart rate and mydriasis (Mas et al. 1999). Modest increases in temperature were observed in some studies but not in others (Mas et al. 1999; de la Torre et al. 2000b; Liechti et al. 2000a, 2000b; Tancer et al. 2003). Subjective effects of MDMA are characterised by euphoria and wellbeing. Mild changes in body perception, including visual and auditory alterations are observed but no hallucinogenic or psychotic episodes usually occur (Camí et al. 2000). MDMA increases plasma concentrations of ACTH, cortisol, prolactin and vasopressin (Grob et al. 1996; Henry et al. 1998; Vollenweider et al. 1998; Mas et al. 1999). Acute severe toxic effects induced by ecstasy include hyperthermia, hyponatremia, multiorganic failure, rhabdomyolisis, disseminated intravascular coag-

ulation and serotonin syndrome, which can ultimately lead to death (Kalant 2001; Camí and Farré 2003). In animals, the administration of a single high dose or repeated dosing of MDMA to rats and primates produce a neurodegeneration of the serotonergic system (Rothman and Baumann 2002). In mice, MDMA induces neurodegeneration of the dopaminergic system, similar to that produced by methamphetamine (Green et al. 2003). The impact of this neurodegeneration on subjects consuming ecstasy is the most worrisome issue of its misuse. Some clinical studies have observed a gradual loss of some cognitive functions (memory, performance of complex tasks), a higher impulsivity (may be translated as aggressiveness and violent behaviour), and to some extent a larger incidence of psychopathology among users of such substances (depression among others). However, the interpretation of these results is limited by their study design (cross-sectional) (Morgan et al. 1999, 2000).

The mean number of ecstasy tablets taken in a typical episode of consumption (or session) ranges from 1 to 2.8 tablets. More than 44% of users take more than one tablet in each session and 25% of them usually take 4 or more tablets on some occasions (Topp et al. 1999; Winstock et al. 2001). Most users take 1 tablet at the beginning and then repeat the administration at different intervals in order to achieve the desired effects during a long period of time ("boosting"), but some take various tablets at one time ("stacking") (Hammersley et al. 1999). These patterns of use may lead to increased risk of both acute and mid/long-term toxicity. MDMA shows non-linear pharmacokinetics in humans (de la Torre et al. 2000a), and it seems that MDMA could inhibit its own metabolism by interacting with cytochrome P-450 2D6 (CYP2D6) (Delaforge et al. 1999).

Although repeated administration of MDMA is very common, the administration of two or more doses of MDMA has never been studied in a controlled clinical setting. Due to the inhibition of its own metabolism, one previous dose could modify the pharmacokinetic parameters and metabolic profile of the following dose. In the case of other amphetamines, the administration of repeated doses produced acute tolerance to some effects and enhancement or sensitisation of others (Comer et al. 2001; Strakowski et al. 2001)

As a first attempt to study the effects and pharmacokinetics of MDMA after repeated doses, a study was designed in which subjects were administered two consecutive doses of MDMA separated by 24 h.

Materials and methods

Volunteers

The study was conducted in accordance with the Declaration of Helsinki, approved by the local Institutional Review Board (CEIC-IMAS), and authorised by the Dirección General de Farmacia y Productos Sanitarios (98/112) of the Spanish Ministry of Health. All volunteers gave their written informed consent before inclusion in the study and were paid for their participation in the experimental sessions.

Male volunteers were recruited by word of mouth. Eligibility criteria required the recreational use of MDMA on at least five occasions. Each eligible subject was initially interviewed by a physician to exclude concomitant medical conditions, and underwent a general physical examination, routine laboratory tests, urinalysis, and 12-lead ECG. Volunteers who fulfilled the inclusion criteria were then interviewed by a psychiatrist (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV, DSM-IV) to exclude individuals with history or actual major psychiatric disorders (schizophrenia, psychosis, and major affective disorder). Ten healthy male subjects were included in the study. Subjects were phenotyped for CYP2D6 activity by using dextromethorphan as a drug probe (Schmidt et al. 1985). All prospective volunteers, but one, were extensive metabolizers according to their urinary dextromethorphan/dextrorphan ratio. This individual is excluded from the results presented here. Data here presented refer to the nine volunteers who took part in the final study. They had a mean age of 23 years (range 21–33), mean body weight of 73.3 kg (range 60.6–86.5), and mean height of 177 cm (range 168–189). They reported an average of 26 previous experiences (range 6–100) with MDMA. All but two subjects were current smokers. None had a history of abuse or drug dependence according to DSM-IV criteria (except for nicotine dependence). All had previous experience with other psychostimulants, cannabis or hallucinogens. None had a history of adverse medical or psychiatric reactions after MDMA consumption.

Drugs

(*R*,*S*)-MDMA was supplied by the Spanish Ministry of Health and prepared by the Pharmacy Department of our institution as identically appearing opaque, white, soft gelatine capsules. The two drug conditions in the study were as follows: 100 mg MDMA on day 1 followed by 100 mg MDMA on day 2 (24 h later) and placebo plus placebo also with the same dosing interval.

Study design

Subjects participated as outpatients in two experimental sessions each two days in length with at least 1-week washout period between each session. A training period of 4–5 h was necessary before starting study sessions to familiarise volunteers with testing procedures and questionnaires, and to achieve a steady performance in the psychomotor tasks. The study design was double blind, randomised, crossover, and controlled with placebo.

At the beginning of each day of each session, subjects arrived at the laboratory at 8:00 a.m. after an overnight fast. An indwelling intravenous catheter was inserted into a subcutaneous vein in the forearm of the non-dominant arm and 0.9% sodium chloride solution was infused at a rate of 20 ml/h. Thereafter, they remained seated in a quiet room throughout the session. Drugs were administered at 9:30 a.m. (MDMA or matched placebo). A light meal was provided 6 h after MDMA administration. Tobacco smoking was permitted 6 h after drug administration. Subjects were requested to refrain from consuming any drug 2 weeks before and throughout the duration of the study. At each session and before drug administration, urine samples were collected to check by immunological methods (FPIA; Abbott Laboratories, Chicago, Ill., USA) the use of drugs of abuse (opiates, cocaine metabolite, amphetamines, and cannabinoids).

Physiological measures

Non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, oral temperature and pupil diameter were recorded

at −15 min and immediately before drug administration (time 0, baseline) and at 20, 40, 60, and 90 min, and at 2, 3, 4, 6, 8, 10, 24 h after each drug administration using a DinamapTM 8100-T vital signs monitor (Critikon, Tampa, Fla., USA). For safety reasons, ECG was continuously monitored during all the session using a DinamapTM Plus vital signs monitor (Critikon). Pupil diameter was recorded with a Haab pupil gauge (Pickworth et al. 1998).

Psychomotor performance measures

Psychomotor performance battery included the simple reaction time, the digit symbol substitution test (DSST), and the Maddox-wing device. This battery has been used previously in the evaluation of psychostimulants and MDMA effects (Farré et al. 1993; Camí et al. 2000; de la Torre et al. 2000a, 2000b; Hernández-López et al. 2002). 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 (simple reaction time). The DSST is a subtest of the Wechsler Adult Intelligence Scale—Revised. (Wechsler et al. 1958). A computerized version was used (McLeod et al. 1982), and scores were based on the number of correct patterns keyed in 90 s (correct responses). The Maddox-wing device measures the balance of extraocular muscles and quantifies exophoria, as an indicator of extraocular musculature relaxation, and esophoria. Results were expressed in diopters along the horizontal scale of the device. (Hannington-Kiff 1970). The psychomotor performance battery was performed at 0 h (immediately before drug administration) and 60 and 90 min, and at 2, 3, 4, 6, 8, 10, and 24 h after each drug administration.

Subjective effects

Subjective effects were measured using a set of 21 different visual analogue scales (VAS), and the Addiction Research Center Inventory (ARCI). A total of 21 visual analogue scales (100 mm) labelled with different adjectives marked at opposite ends with "not at all" and "extremely" were used (Camí et al. 2000). Subjects were asked to rate effects of "stimulated", "high", "any effect", "good effects", "bad effects", "liking", "drowsiness", "changes in distances", "changes in colours", "changes in shapes", "changes in lights", "hallucinations-seeing of lights or spots", "changes in hearing", "hallucinations-hearing sounds or voices", "dizziness", "hallucinations-seeing animals, things, insects or people", "confusion", "fear", "depression or sadness", "different, changed or unreal body feeling", and "different or unreal surroundings". Scales were administered at 0 h (before drug administration), and at 20, 40, 60 and 90 min, and at 2, 3, 4, 6, 8, 10, and 24 h after drug administration. ARCI is a true–false questionnaire with empirically derived scales that are sensitive to the effects of a variety of classes of drugs of abuse (Martin et al. 1971; Haertzen 1974). The Spanish validated version of a 49-item short form of ARCI was used (Lamas et al. 1994). The questionnaire included five scales: PCAG (pentobarbital-chlorpromazine-alcohol group, a measure of sedation); MBG (morphine-benzedrine group, a measure of euphoria); LSD (lysergic acid dyethylamine group, a measure of dysphoria and somatic symptoms); BG (benzedrine group, a stimulant scale consisting mainly of items relating to intellectual efficiency and energy); and A (amphetamine, an empirically derived scale sensitive to the effects of *d*-amphetamine). ARCI was administered at 0 h (immediately before drug administration), and at 20, 40, 60 and 90 min, and at 2, 3, 4, 6, 8, 10 and 24 h after each drug administration.

Cortisol and prolactin concentrations

Blood samples for determination of cortisol and prolactin were collected during each experimental sessions at baseline and at 20, 40, 60 and 90 min, and at 2, 3, 4, 6 h after drug administration. Plasma cortisol concentrations were determined by fluorescence polarization immunoassay (FPIA) (Abbott Laboratories) according to the manufacturer's instructions. Prolactin plasma concentrations were determined by a microparticle enzyme immunoassay (MEIA) (Abbott Laboratories) using an IMxR instrument and following the manufacturer's instructions. Details of both assays have been previously published (Farré et al. 1997; Mas et al. 1999; de la Torre et al. 2000a, 2000b).

MDMA and MDA concentrations

Blood samples for determination of MDMA and MDA (3,4-methylenedioxyamphetamine) plasma concentrations were collected during each experimental sessions at baseline and at 20, 40, 60 and 90 min, and at 2, 3, 4, 6, 8, 10, 24 h after drug administration. Urine samples were collected in the following intervals: 0–4, 4–8, 8–12, 12–24 h after drug administration. In order to evaluate elimination kinetics additional samples of plasma were collected at 30 and 48 h after second administration, and urine was collected at 48–54 and 54–72 h from the beginning of the experimental session. Plasma MDMA and MDA concentrations were measured by gas chromatography coupled to mass spectrometry (Pizarro et al. 2002).

Data analysis

Values from pharmacological effects (psychomotor performance measures, subjective variables and hormone concentrations) were transformed to differences from baseline. For each variable, the peak effect in the first 6 h following each administration (maximum absolute change from baseline values) and the 6 h area under the curve (AUC) of effects versus time, calculated by the trapezoidal rule, were determined. These transformations (peak effect and AUC) were analysed by a two-way repeated measures analysis of variance (ANOVA) with drug conditions (MDMA or placebo) and administration (first and second dose) as factors. When ANOVA results showed significant effects for drug condition or drug condition-administration, post-hoc multiple comparisons were performed using the Tukey's test. Furthermore, a detailed comparison of time-course of effects was conducted using repeated measures three-way ANOVA with drug condition, administration and time (from 0 to 6 h) as factors. When drug condition, drug condition×administration, drug condition×time or drug condition×administration×time interactions were statistically significant, multiple Tukey post-hoc comparisons were performed at each time point using the mean square error term of the drug condition×administration×time interaction. Differences associated with *P*-values lower than 0.05 were considered to be statistically significant.

With regard to plasma concentrations of MDMA and MDA, the following parameters were calculated: peak concentration (C_{max}), time taken to reach peak concentration (t_{max}), area under the concentration-time curve from 0 to 24 h, and 0 to infinity after drug administration. The AUC values were calculated by the trapezoidal rule. Pharmacokinetic parameters of MDMA and MDA including elimination constant and elimination half-life were calculated using a computer program (PKCALC) (Shumaker 1986). The paired Student's *t*-test (C_{max} and AUC) and the Wilcoxon test (t_{max}) were used for statistical analysis. Differences associated with *P*-values lower than 0.05 were considered to be statistically significant.

Results

Table 1 shows results of the variables where a significant differences statistical comparison was found in the ANOVA analysis between treatment conditions (peak,

AUC, time-course). Figures 1, 2, 3, 4 and 5 show the time course of variables evaluated.

Pharmacological effects

Placebo administration did not produce notable differences compared with baseline values. Administration of first and second placebos produced similar effects in all variables measured. Differences between both placebos were found at three anecdotal points during the time course-effects on DSST (3 and 6 h) and Maddox-Wing (3 h) (Table 1).

Both administrations of MDMA produced significant effects in comparison to placebo when considering the peak effects and AUC ($P<0.05$, drug condition factor in ANOVA) and time-course ($P<0.05$, drug condition-time factor in ANOVA) of those variables that define the prototypical effects of MDMA (Table 1). MDMA administration produced a significant increase on SBP, DBP and HR, and induced mydriasis. The increase observed in HR after 6 h in all treatments could be explained by smoking and meals. The total number of DSST responses slightly decreased after MDMA, producing esophoria in the Maddox-Wing device. The administration of MDMA increased all subjective measures related to stimulation, euphoria (e.g. VAS-high, ARCI-MBG) and wellbeing. MDMA also induced mild changes in VAS "changes in colours", "changes in lights", "different, changed or unreal body feeling", and the ARCI-LSD scale. No statistically significant differences were found between MDMA and placebo in temperature or reaction time and subjective variables related to bad effects, sedation, and hallucinations. MDMA induced an increase in cortisol and prolactin during 4 h after administration (Table 1).

In reference to the comparison of interest in this study, that between both MDMA administrations [MDMA-first dose (MDMA-1) and MDMA-second dose (MDMA-2) administered 24 h later] the differences were as follows.

In reference to physiological parameters, MDMA-2 produced a higher increase in SBP and DBP in comparison to MDMA-1. The peak increase after MDMA-2 in SBP was 34 mmHg and after MDMA-1 was 25 mmHg. The peak increase after MDMA-2 in DBP was 20 mmHg and after MDMA-1 was 10 mmHg. The increases in SBP/DBP were only statistically significant in some points of the time-course during the first 2 h after administration (Fig. 1). MDMA-2 slightly increased HR in comparison to MDMA-1, but the result was only significant at 40 min after administration. The peak increase of HR from baseline after MDMA-2 and MDMA-1 were 22 bpm and 16 bpm, respectively. Diagnostic criteria of isolated systolic hypertension (>140 mmHg) were met by six subjects following the first dose of MDMA and eight subjects following the second. Hypertensive episodes showed a mean duration of 1 h (range 0.5–2) following the first dose and 1.4 h (range 0.5–3) following the second dose. On the other hand, two subjects met diagnostic criteria of sinus tachycardia (>100 beats/min), both following the second dose of MDMA. Tachycardia lasted between 15 and 30 min.

Although temperature slightly increased following both doses of MDMA, as mentioned previously no statistically significant differences were observed compared to placebo or between doses. In relation to pupil diameter, both doses of MDMA produced similar mydriasis, without statistically significant differences between both doses.

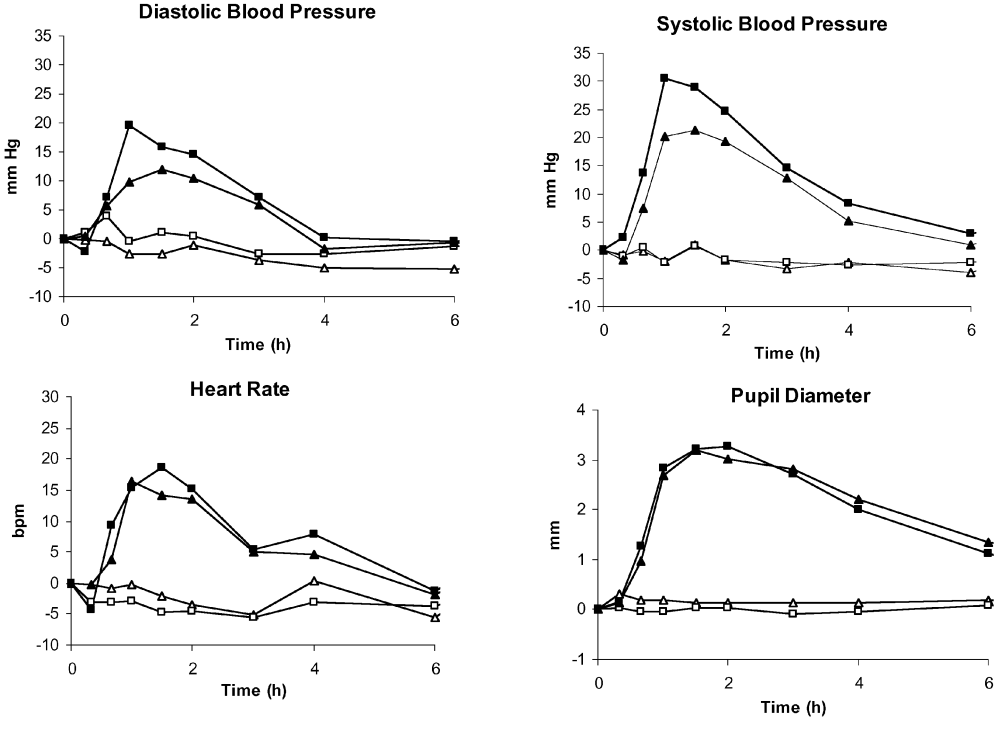

Fig. 1 Physiological effects following two repeated doses of 100 mg MDMA over a period of 24 h (n=9). MDMA 0–24 h (-▲-), placebo 0–24 h (-○-), MDMA 24–48 h (-■-), placebo 24–48 h (-□-)

Table 1 Results of statistical analysis of variables that presented significant differences between placebo and/or between MDMA doses. *AUC* area under the curve, 0–6 h, *Peak* peak effects from 0 to 6 h; *MDMA-1* first dose of 3,4-methylenedioxymethamphetamine; *MDMA-2* second dose of 3,4-methylenedioxymethamphetamine; *Placebo-1* placebo for first dose; *Placebo-2* placebo for second dose; *F* ANOVA *F*-value (*df* 1,8); *P* statistical significance level; Tukey test statistical significance

Variable		ANOVA (*df* 1,8)		Tukey multiple comparison test			
		F	*P*-value	Placebo-1 Placebo-2	Placebo-1[a] MDMA-1	Placebo-2[a] MDMA-2	MDMA-1 MDMA-2
Physiological parameters							
SBP	AUC	78.129	<0.001	NS	**	**	NS
	Peak	212.909	<0.001	NS	**	**	NS
	Time	34.637	<0.001	NS	0.66–6 h[b]	0.66–6 h	0.66–2 h
DBP	AUC	7.643	0.024	NS	*	*	NS
	Peak	13.405	0.006	NS	*	**	NS
	Time	12.825	<0.001	NS	0.66–3 h	1–3 h	1 h
HR	AUC	39.323	<0.001	NS	**	**	NS
	Peak	34.606	<0.001	NS	**	**	NS
	Time	15.188	<0.001	NS	1–3 h	0.66–4 h	0.66 h
Temp	AUC	3.872	0.085	–	–	–	–
	Peak	1.176	0.310	–	–	–	–
	Time	8.220	<0.001	NS	NS	NS	NS
Maddox	AUC	10.363	0.012	NS	**	**	NS
	Peak	8.765	0.018	NS	**	**	NS
	Time	5.297	<0.001	3 h	1–6 h	1–3 h	NS
PD	AUC	66.380	<0.001	NS	**	**	NS
	Peak	88.212	<0.001	NS	**	**	NS
	Time	40.650	<0.001	NS	0.66–6 h	0.66–6 h	NS
Psychomotor performance							
DSST total	AUC	5.350	0.049	NS	NS	NS	NS
	Peak	3.653	0.092	–	–	–	–
	Time	4.818	0.001	3 h, 6 h	1–1.5 h, 3 h	1–1.5 h	NS
VAS							
Stimulated	AUC	92.453	<0.001	NS	**	**	*
	Peak	58.490	<0.001	NS	**	**	*
	Time	31.313	<0.001	NS	1–2 h	0.66–2 h	1–1.5 h
High	AUC	45.493	<0.001	NS	**	**	NS
	Peak	34.384	<0.001	NS	**	**	NS
	Time	21.476	<0.001	NS	1–2 h	0.66–2 h	1 h
Any effects	AUC	67.477	<0.001	NS	**	**	NS
	Peak	51.643	<0.001	NS	**	**	NS
	Time	29.100	<0.001	NS	1–2 h	1–2 h	1 h
Good effects	AUC	63.175	<0.001	NS	**	**	NS
	Peak	45.168	<0.001	NS	**	**	NS
	Time	24.408	<0.001	NS	0.66–2 h	0.66–2 h	NS
Liking	AUC	58.569	<0.001	NS	**	**	NS
	Peak	38.400	<0.001	NS	**	**	NS
	Time	18.083	<0.001	NS	0.66–2h	0.66–2h	NS
Changes in colours	AUC	8.140	0.021	NS	NS	NS	NS
	Peak	7.314	0.027	NS	NS	NS	NS
	Time	2.831	0.009	NS	1 h	1 h	NS
Changes in lights	AUC	11.344	0.010	NS	**	**	NS
	Peak	10.434	0.012	NS	**	**	*
	Time	7.099	<0.001	NS	1–1.5 h	0.66–1.5 h	1 h
Changes in hearing	AUC	3.174	0.113	–	–	–	–
	Peak	3.317	0.106	–	–	–	–
	Time	2.508	0.019	NS	1–1.5 h	1 h	1 h
Body Sensation	AUC	14.789	0.005	NS	**	**	NS
	Peak	25.379	0.001	NS	**	**	NS
	Time	11.090	<0.001	NS	1–2h	0.66–2h	NS

*$P<0.05$; **$P<0.01$; *NS* not significant.*Blank* ANOVA result non-significant, and Tukey test was not performed

[a]Active conditions are compared with their own temporal placebo

[b]Values represent significant differences at points along the time versus effect curve (units are hours)

Table 1 (continued)

Variable		ANOVA		Tukey multiple comparison test			
		(*df* 1,8)		Placebo-1	Placebo-1[a]	Placebo-2[a]	MDMA-1
		F	*P*-value	Placebo-2	MDMA-1	MDMA-2	MDMA-2
ARCI questionnaires							
ARCI-PCAG	AUC	0.044	0.838	–	–	–	–
	Peak	0.473	0.511	–	–	–	–
	Time	6.597	<0.001	NS	NS	1–1.5 h, 3–4 h	1 h, 3 h
ARCI-MBG	AUC	23.717	0.001	NS	**	**	NS
	Peak	44.924	<0.001	NS	**	**	NS
	Time	16.290	<0.001	NS	0.66–3 h	0.66–3 h	0.66 h
ARCI-LSD	AUC	11.808	0.009	NS	**	**	*
	Peak	12.779	0.007	NS	**	**	NS
	Time	13.702	<0.001	NS	0.66–2 h	0.66–3 h	1.5 h, 3 h
ARCI-BG	AUC	16.148	0.004	NS	*	**	NS
	Peak	26.510	0.001	NS	NS	*	NS
	Time	10.717	<0.001	NS	0.66–2 h	0.66–2 h	1 h
ARCI-A	AUC	39.116	<0.001	NS	**	**	NS
	Peak	48.460	<0.001	NS	**	**	NS
	Time	17.806	<0.001	NS	0.66–3 h	0.66–3 h	NS
Hormones							
Cortisol	AUC	155.041	<0.001	NS	**	**	*
	Cmax	140.655	<0.001	NS	**	**	NS
	Time	59.648	<0.001	NS	1–4 h	1–4 h	1–2 h, 4–6 h
Prolactin	AUC	27.572	0.001	NS	**	**	NS
	Cmax	28.943	0.001	NS	**	**	NS
	Time	16.300	<0.001	NS	1–4 h	1–4 h	NS

Psychomotor performance results are shown in Fig. 2. In the DSST task, both doses slightly decrease the total number of DSST responses, but no differences were found between MDMA doses. MDMA did not produce significant effects on reaction time. Both doses produced similar levels of esophoria in the Maddox wing device.

Subjective effects after administrations of drug conditions are shown in Fig. 3 and Fig. 4. Although MDMA-2 produced a relative increase in the scores of most subjective effects in comparison to MDMA-1, the results were statistically significant in few scales. MDMA-2 produced a significant increase in comparison to MDMA-1 on the scores of "stimulated" (peak, AUC, time-course), "high" (time-course), "any effect" (time-course), "changes in lights" (peak, time-course), "changes in hearing" (time-course), ARCI-PCAG (time-course), ARCI-MBG (time-course), ARCI-LSD (AUC, time-course), and ARCI-BG (time-course). In comparison to MDMA-1, the administration of MDMA-2 slightly increased the pleasant-related effects, increased stimulation, decreased sedation, modified perception of lights and hearing, and produced an augmentation of physical sensations. Neither MDMA-2 nor MDMA-1 produced hallucinations or psychotic symptoms.

Plasma hormone concentrations over time curves are shown in Fig. 5. The second dose of MDMA produced a statistically significant increase of cortisol in comparison to the first dose. The maximal concentration and AUC increased approximately 49% and 75%, respectively. The C_{max} after MDMA-2 was 21.08 μg/ml, and after MDMA-1 of 14.11 μg/ml. No differences were seen in prolactin response between doses of MDMA.

Pharmacokinetics

Plasma concentrations over the time curves of MDMA and MDA are presented in Fig. 6. Fig. 6 also shows the urinary elimination of MDMA and MDA. Table 2 shows the pharmacokinetic parameters of MDMA and MDA in plasma.

For MDMA, at the time point of 24 h after the administration of the first dose of MDMA, most of the subjects presented quantifiable concentrations of MDMA (mean concentration=12 ng/ml). The C_{max} after the first and second administrations were 180 ng/ml and 232 ng/ml, respectively. That represents an increase of 29%. The increase in the AUC was 77%. The elimination constant decreased and elimination half-life increased after the second MDMA administration. Following the second dose, plasma concentrations for MDA increase 64% in the AUC and 40% in the C_{max}. Observations made in urine further confirm plasma concentration findings, with higher recoveries of MDMA and MDA after the second dose.

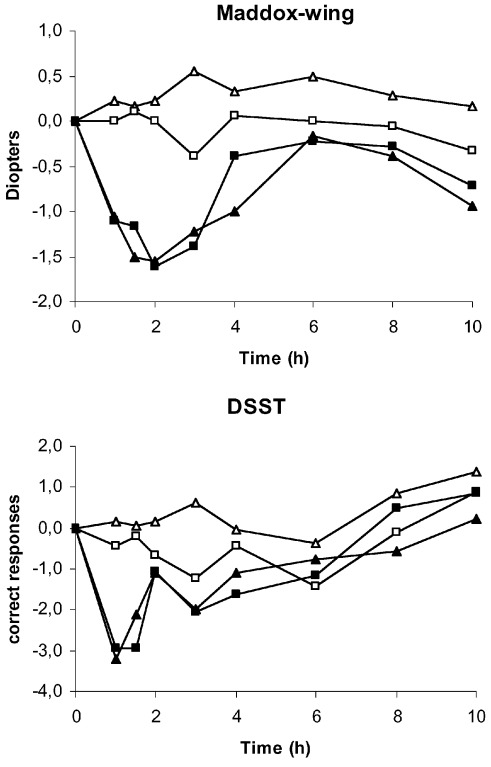

Fig. 2 Psychomotor performance parameters following two repeated doses of 100 mg MDMA over a period of 24 h (n=9). MDMA 0–24 h (-▲-), placebo 0–24 h (-○-), MDMA 24–48 h (-■-), placebo 24–48 h (-□-)

Discussion

Repeated administration of MDMA produced a disproportionate increase in plasma concentrations in MDMA and MDA due a combination of simple accumulation of the drug and metabolic inhibition. The pharmacological effects after the second administration were slightly higher than those following the first but lower than expected considering the MDMA concentrations achieved following the second dose.

The administration of a single dose of 100 mg MDMA produced the typical effects described for this substance in an experimental laboratory setting (Mas et al. 1999; de la Torre et al. 2000a, 2000b; Lester et al. 2000; Harris et al. 2002; Hernández-López et al. 2002; Tancer et al. 2003). MDMA increased blood pressure and heart rate, produced mydriasis and induced extraocular muscular tension (esophoria). As observed in other studies, MDMA did not produce a significant increase of temperature in comparison to placebo (Vollenweider et al. 1998; Mas et al. 1999; Hernández-López et al. 2002). The administration of MDMA produced feelings of stimulation, euphoria, liking and wellbeing. Only small changes in perception of lights and sounds were observed. No hallucinations or psychotic symptoms were observed. These results are similar to those described in previous investigations using equivalent doses (Mas et al. 1999; Hernández-López et al. 2002). MDMA slightly reduced the number of total

Table 2 Pharmacokinetics of MDMA and metabolites following two repeated doses of 100 mg MDMA over a period of 24 h (n=9)

	AUC_{0-24} (ng/ml.h^{-1})	$Cmax_{0-24}$ (ng/ml)	AUC_{24-48} (ng/ml.h^{-1})	$Cmax_{24-48}$ (ng/ml)	$Tmax_{0-24}$ (h) median	$Tmax_{24-48}$ (h) median	Ke_{0-24} (h^{-1})	Ke_{24-48} (h^{-1})	$t_{1/2\ (0-24)}$ (h)	$t_{1/2(24-48)}$ (h)	AUC_{24-48} /AUC_{0-24}	$Cmax_{24-48}$ / $Cmax_{0-24}$
MDMA	1452	180	2564	232	2	25.5	0.112	0.081	7.0	8.8	1.77*	1.29*
SD	771	33	762	39	0.26	0.33	0.054	0.017	2.2	1.5	77%	29%
MDA	157	11	259	15	4	28	0.056	0.052	12.8	14.1	1.64*	1.40*
SD	55	3	81	4	6.88	2.71	0.012	0.013	2.9	3.4	64%	40%

*P≤0.001, results from a paired Student'st-test present differences between first and second doses

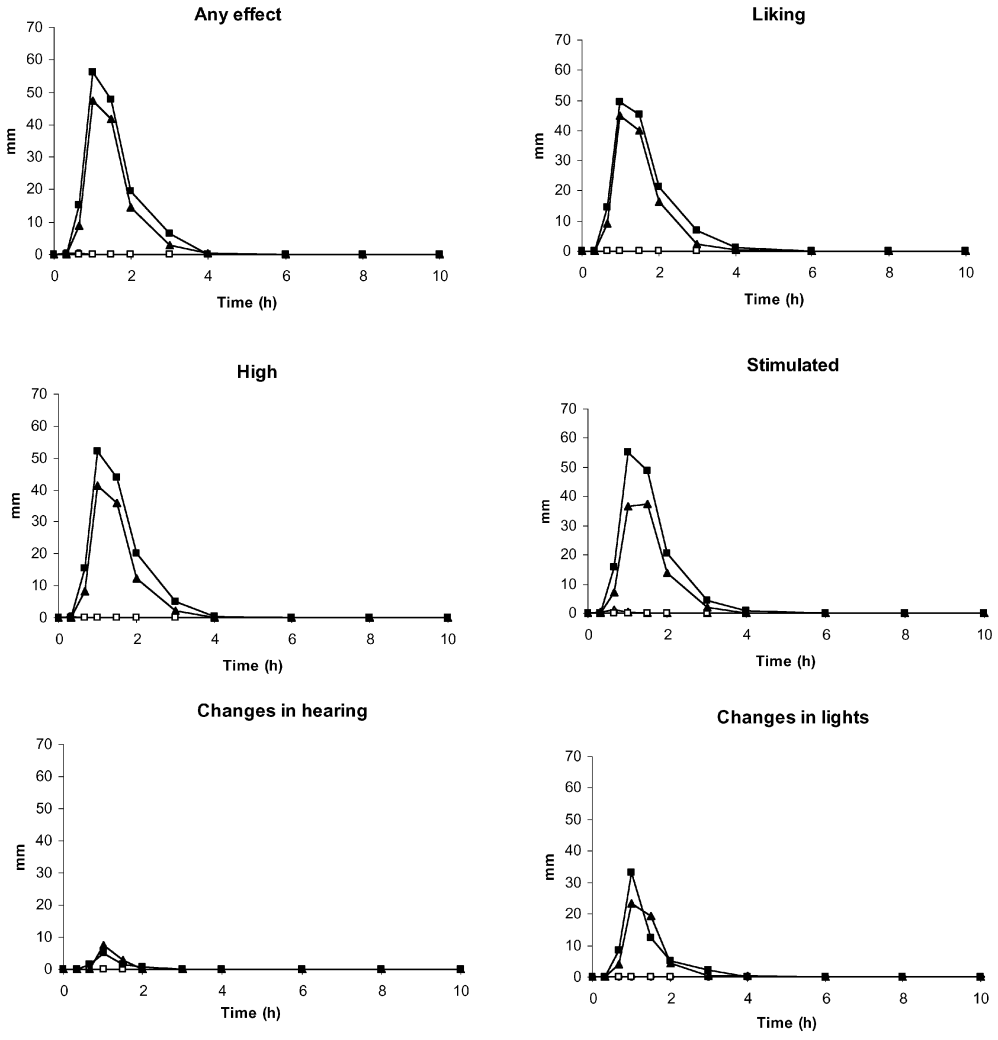

Fig. 3 Visual analog scale measurements for subjective effects following two repeated doses of 100 mg MDMA over a period of 24 h (n=9). MDMA 0–24 h (-▲-), placebo 0–24 h (-○-), MDMA 24–48 h (-■-), placebo 24–48 h (-□-)

responses in the DSST but these changes were not significant. In a previous study where an identical dose of MDMA (100 mg) was administered in combination with ethanol no impairment of performance was produced (Hernández-López et al. 2002), but a higher dose (125 mg) produced similar reductions as observed in the present study (Camí et al. 2000). It is interesting to comment that in the present work, sedation measured by the ARCI-PCAG was reduced but in other studies, sedation increased when a 125 mg dose was administered (Camí et al. 2000). Differences in the study design or in the subjects selected can explain changes observed in subjective sedation.

To our knowledge, the results of this study are the first published in the literature concerning repeated administration of MDMA in an experimental setting. The effects observed following the second dose must be interpreted taking the plasma concentrations of MDMA from the first dose into account. The maximal concentrations of MDMA observed after the first dose were in the range of those described following the administration of 100 mg in previous studies (de la Torre et al. 2000a, 2000b; Hernández-López et al. 2002). Similar levels of the metabolite MDA were obtained when the same dose of MDMA was administered in previous investigations (de la Torre et al. 2000a, 2000b).

The maximal concentrations of MDMA obtained following the second dose were similar to those obtained after the administration of a dose of 125 mg in a previous study (232 ng/ml versus 236 ng/ml, respectively) (Mas et al. 1999). The higher concentrations observed following the second dose (+77% AUC) can not be fully explained considering the simple accumulation obtained by summing the concentrations achieved after the second dose with those present following the first dose of MDMA. It is possible to calculate the contribution of the first dose to the AUC of the second by subtracting the $AUC_{0–24\ h}$ from the $AUC_{0\text{-inf}}$ of the first dose. This portion of the time versus concentration curve is then subtracted from the $AUC_{24–48\ h}$. On calculating the AUC first dose/second dose ratio with this corrected value, an increase of 39% between first and second doses is obtained. This increase is more consistent with changes observed in C_{max}. Similar changes were observed in the study of Mas et al. (1999) when comparing pharmacokinetic data between 75 and 125 mg doses of MDMA. The difference between the expected increase on AUC (39%) and that observed (77%) can be related to the non-linear pharmacokinetics of

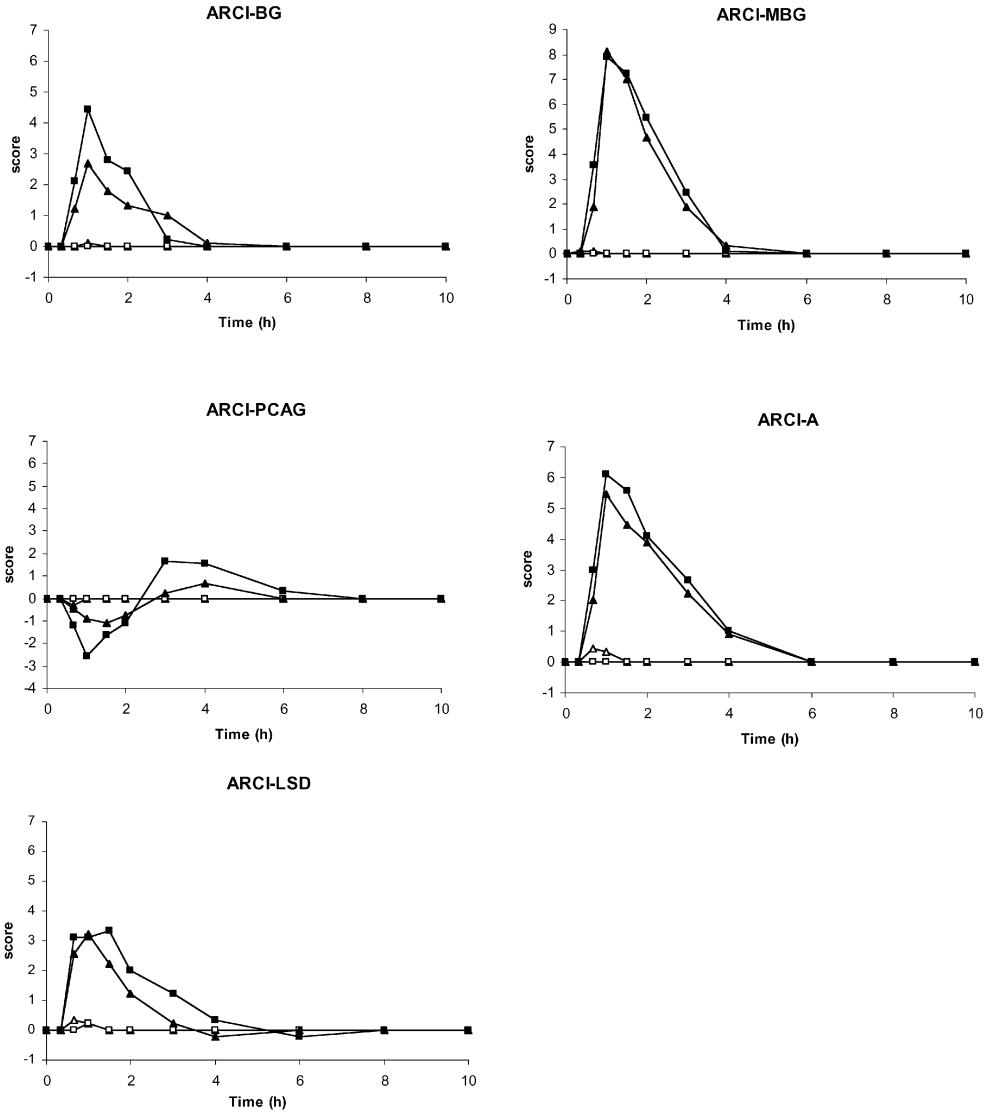

Fig. 4 Time course of two repeated doses of 100 mg MDMA at 0 h and 24 h on ARCI questionnaire subscales (n=9). MDMA 0–24 h (-▲-), placebo 0–24 h (-○-), MDMA 24–48 h (-■-), placebo 24–48 h (-□-)

MDMA in humans already described (de la Torre et al. 2000a, 2000b). The latter hypothesis was based on the results of the administration of single doses of MDMA in the range of 50–150 mg. The present data of unexplained accumulation after two repeated doses confirms this non-linearity. In animals, a recent study has demonstrated accumulation of MDMA following multiple dosing (Bowyer et al. 2003). It is postulated that the methylenedioxy group present in the chemical structure of MDMA is responsible for the auto-inhibition of its metabolism. Indeed, methylenedioxy groups form intermediate metabolite enzyme complexes that quasi-irreversibly inactivate cytochrome P450 both in animals (Ortiz de Montellano et al. 1995) and plants (Schlak et al. 1998). MDMA itself, during its metabolism, has been shown to form a complex with CYP2D6 in vitro (Delaforge et al. 1999). Preliminary results from clinical trials conducted in our department where MDMA was co-administered with the CYP2D6 and SERT inhibitor paroxetine (Farré et al. 2002), a drug also bearing the methylenedioxy group (Bertelsen et al. 2003) have reinforced the theory that MDMA is an inhibitor of CYP2D6, forming an enzyme metabolite complex. An inhibition of MDMA metabolism is evident, and could be responsible at least for the difference of 39% not explained by simple accumulation. The increase shown in MDA plasma concentrations is more related to a higher availability of substrate (MDMA) for N-demethylation rather than to any metabolic interaction. The data in urine are similar to that of plasma, confirming the possible double mechanism responsible for total accumulation (simple accumulation and inhibition).

The pharmacological effects after the second administration were slightly higher than those observed after the first administration in the majority of variables measured in this study. Significantly different effects were only clearly observed in the blood pressure and some subjective effects (stimulated, high, any effects, changes in lights and sounds, changes in hearing, some ARCI scales) and cortisol concentrations. The magnitude of the changes in these parameters was similar to that described when a dose of 125 mg MDMA was administered in a previous study (Mas et al. 1999; Camí et al. 2000). Taking the increase in

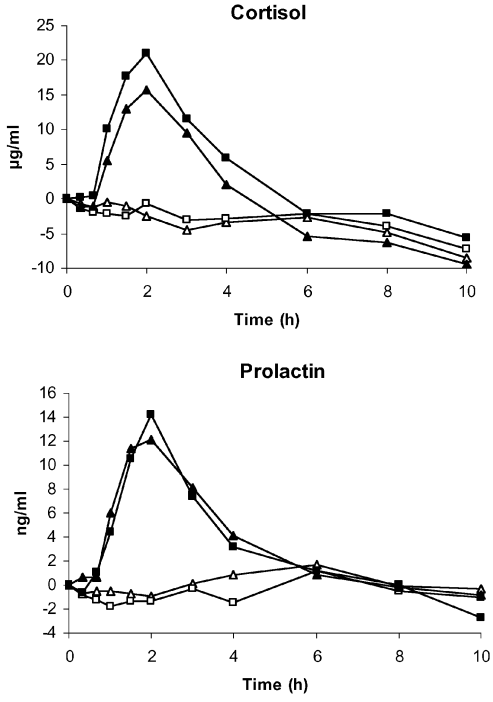

Fig. 5 Plasma concentrations of cortisol and prolactin following two repeated doses of 100 mg MDMA over a period of 24 h (n=9). MDMA 0–24 h (-▲-), placebo 0-24 h (-○-), MDMA 24–48 h (-■-), placebo 24–48 h (-□-)

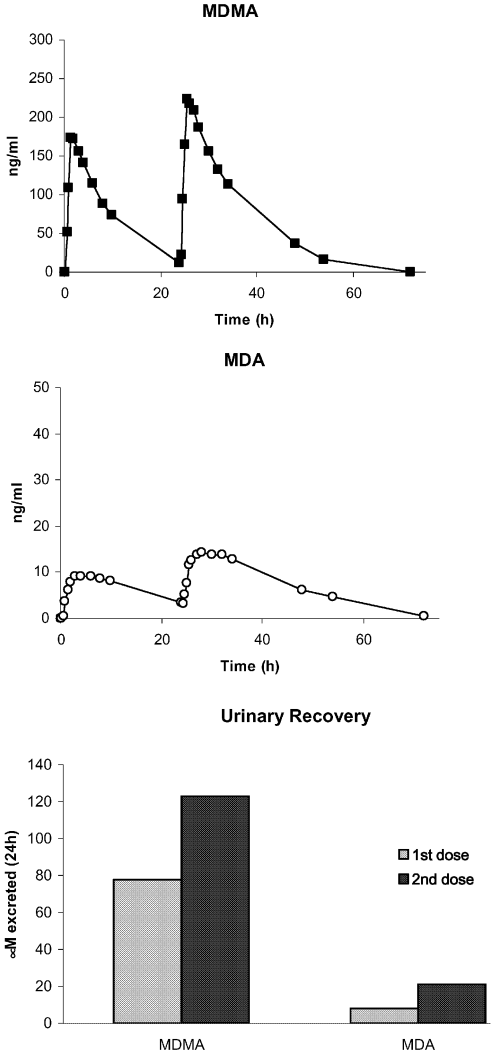

Fig. 6 Plasma concentrations and urinary recovery of MDMA and MDA (n=9)

the plasma concentration of MDMA following the second dose into account (+29% in C_{max} and +77% in AUC), the increases in the above mentioned parameters are lower than expected in most variables. In some variables such as pupil diameter, Maddox-wing, ARCI-A and especially prolactin the effects following the second dose were similar to those of the first dose, suggesting the possible appearance of some degree of tolerance. Rapid or acute tolerance has been described in animals for both MDMA and other amphetamines after a second dose (Frederick et al. 1995) and in humans after the administration of two or more repeated doses of amphetamines (Pérez-Reyes et al. 1991; Comer et al. 2001). MDMA's mechanism of action may explain this phenomenon for some variables. The serotonin exhaustion due to increased release, inhibition of re-uptake and decrease in formation by inhibition of tryptophan hydroxylase following the first dose of MDMA would diminish the amount of neurotransmitter available for release following the second dose (Green et al. 2003).

In experimental animals, the use of amphetamines and cocaine has been associated with the opposite phenomenon, called sensitisation ("kindling"), which manifests itself with the appearance of increased effects following the repetitive administration of doses that did not previously produce this response. In our results, none of the pharmacological effects evaluated show increases above those expected by the dose or concentrations observed.

This study has some limitations. It is possible that the smaller than expected increases in some subjective variables may be due to the tests used. Many of the ARCI parameters are at the upper limit of their scale score. An increase in the concentration of the drug, which may normally cause an increase in effects, may not be detectable by the questionnaires because any additional increases in effects are not possible to describe. These limitations are related to the instruments used or to the organic response that can be applied for example to the mydriasis observed. The increase in pupil diameter probably achieved a ceiling effect that cannot be further enhanced. Another limitation of the study is the number of subjects included, a size of nine participants may not have enough statistical power to show differences in some variables, although statistical differences were found in others. The selected interval between doses of MDMA clearly demonstrated a metabolic inhibition of MDMA metabolism, but it is difficult to extrapolate the results to shorter intervals of administration, i.e. the intervals of administration as practiced in a recreational setting (2–8 h). This study forms part of a series of studies designed to investigate repeated dosing of MDMA at different intervals. As a first step in this series and in order to

maximise the safety of the subjects, it was decided to administer MDMA at longer intervals than those seen in recreational circumstances. It was also postulated that this interval was sufficient to study the auto-inhibition of MDMA metabolism. Preliminary data from a 4-h interval study seem to confirm metabolic inhibition and the appearance of some degree of tolerance in the variables mentioned above (Farré et al, 2001). MDMA is a lipophilic substance that is postulated to cross the blood–brain barrier with ease. However, the relationship between peripheral and cerebral concentrations is unknown.

The changes seen in the concentrations between first and second doses of MDMA may have health consequences for the acute and long-term effects of MDMA. Recent observations have suggested that MDMA acute toxicity is associated with elevated plasma concentrations and doses (Greene et al. 2003). In our study, the number of cardiovascular complications (isolated hypertension and sinus tachycardia) were more frequent after the second dose.

Ecstasy users frequently take more than one dose per session, often to maintain the effects considered as positive while trying to avoid the residual effects. Considering the pharmacokinetics exhibited following two successive doses of MDMA, it may be speculated as to what would occur when more than two doses are administered. The contribution of the previous dose would increase with every successive administration due to the inhibition of CYP2D6, leading to ever increasing plasma concentrations of MDMA with consequent increases in cardiovascular effects and eventual severe acute toxicity. The inhibition of CYP2D6 is also pharmacologically relevant seeing as many other drugs are specifically metabolised by this enzyme. The administration of MDMA as a drug of abuse may produce serious pharmacological interactions by impeding this metabolism. It should be remembered that medications such as amitriptyline, clomipramine, codeine, dextromethorphan, encainide, fluvoxamine, haloperidol, imipramine, metoprolol, risperidone, tamoxifen, venlafaxin and zuclopentixol amongst others are substrates of this isoenzyme (Karash 2000).

The observation that MDMA auto-inhibits its metabolism is a confirmation of what has been suggested by past in vitro and in vivo investigations. From our results, it is postulated that this inhibition lasts at least 24 h. Future studies are necessary to investigate the effects of repeated administration of MDMA at different intervals and to evaluate the exact duration of the metabolic inhibition produced by MDMA.

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