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3,4-Methylenedioxymethamphetamine (Ecstasy) and Alcohol Interactions in Humans: Psychomotor Performance, Subjective Effects, and Pharmacokinetics

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ABSTRACT

3,4-Methylenedioxymethamphetamine (MDMA) is frequently consumed in association with alcohol. The effect of this combination in humans has not been previously investigated. Nine male healthy volunteers received single oral doses of 100 mg of MDMA plus 0.8 g/kg ethanol, 100 mg of MDMA, 0.8 g/kg of ethanol, and placebo in a double blind, double dummy, randomized crossover trial. Measurements included psychomotor performance, subjective effects, and pharmacokinetics. Plasma concentrations of MDMA showed a 13% increase after the use of alcohol, whereas plasma concentrations of alcohol showed a 9 to 15% decrease after MDMA administration. The MDMA-alcohol combination induced longer lasting euphoria and well being than MDMA or alcohol alone. MDMA reversed the subjective sedation induced by alcohol but did not reduce drunkenness feelings. MDMA did not reverse the actions of alcohol on psychomotor abilities. Combined use of MDMA and alcohol causes dissociation between subjective and objective sedation. Subjects may feel euphoric and less sedated and might have the feeling of doing better, but actual performance ability continues to be impaired by the effect of alcohol. Confirmation of these findings in further studies will be highly relevant in terms of road safety.

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a phenylethylamine structurally similar to amphetamine and mescaline. The drug induces feelings of euphoria, friendliness, closeness to others, and empathy and has been named "entactogen" (Hermle et al., 1993). This drug's ability explains its increasing popularity as a recreational drug during the mid-1970s and 1980s until suggestion of possible neurotoxicity led the Drug Enforcement Administration to include MDMA in Schedule I classification in 1985. The WHO Expert Committee of Drug Dependence also recommended the inclusion of MDMA in List I of the Psychotropic Convention and the substance became definitively illegal in 1986. In spite of the illegal status, recreational use of MDMA has dramatically increased among young people at dance clubs and "raves", with lifetime prevalence rates in adolescents of 0.2% in Finland and 8.3% in the United Kingdom (Pedersen and Skrondal, 1999). It was estimated that ecstasy users in England and Scotland were near to half-million during 1996 (Gore, 1999).

Animal studies in rats and primates have shown that MDMA acts as a serotonergic neurotoxin (Ricaurte et al., 2000). Repeated administration of high oral doses of MDMA may produce long-term reductions in serotonergic activity and degeneration of serotonergic neurons in humans. Chronic heavy use of ecstasy seems to be associated with persistent psychological deficits and cognitive impairment (Morgan, 2000).

MDMA is frequently used in combination with psychoactive drugs. It seems that in young people, alcohol consumption enhances the risk for MDMA use (Pedersen and Skrondal, 1999). A recent survey in Australia showed that 40% of users consumed alcohol concomitantly, with more than 50 g of ethanol in 41% of the cases (Topp et al., 1999). In a survey carried out in Spain, simultaneous consumption of alcohol and MDMA was reported by 64% of interviewees (Gamella et al., 1997). MDMA has been implicated in fatal traffic accidents probably due to impairment in driving-related tasks and potentiation of risky driving (Henry et al., 1992; Hooft and van de Voorde, 1994). Although studies designed to assess the role of MDMA and alcohol combination in terms of road safety have not been carried out, MDMA

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ABBREVIATIONS: MDMA, 3,4-methylenedioxymethamphetamine; DSST, digit-symbol substitution test; ARCI, Addiction Research Center Inventory; VAS, visual analog scale; PCAG, pentobarbital chlorpromazine alcohol group; MBG, morphine benzedrine group; LSD, lysergic acid diethylamine group; BG, benzedrine group; A, amphetamine; AUC, area under the curve; ANOVA, analysis of variance.

administration in experimental conditions was followed by difficulties in concentration and mathematical calculations (Downing, 1986), as well as by marked euphoria and well being with slight impairment in the performance of psychomotor tasks (Camí et al., 2000a). Other stimulants, such as amphetamine and amphetamine derivatives seem to increase the number of car crashes and fatalities associated with accidents when used by alcohol-positive drivers (Sjogren et al., 1997; Schepens et al., 1998; Timby et al., 1998).

A number studies in the laboratory setting have assessed the interaction between alcohol and stimulants with inconclusive results, including the following combinations: ethanol and caffeine (Kerr et al., 1991), ethanol and cocaine (Perez-Reyes and Jeffcoat, 1992; Farré et al., 1993, 1997; Higgins et al., 1993; McCance-Katz et al., 1993), and ethanol and dextroamphetamine or metamphetamine (Perez-Reyes et al., 1992; Mendelson et al., 1995). Although in some studies, stimulants reduced the intoxication ratings, the drunkenness scores, or the deleterious effects of alcohol on psychomotor performance, significant pharmacological changes were not found in other investigations. In reference to amphetamines, the coadministration of alcohol could result in a pharmacokinetic interaction. Oral intake of alcohol increased the concentrations of dextroamphetamine when given by the oral route (Perez-Reyes et al., 1992) and decreased the volume of distribution of methamphetamine when given intravenously (Mendelson et al., 1995).

The interaction between MDMA and alcohol in humans has not been previously investigated. In two studies in rats (Bilsky et al., 1990; Rezvani et al., 1992), acute or repeated administration of MDMA attenuated the consumption of alcoholic beverages, but did not produce changes in plasma concentrations of ethanol. The present double blind, double dummy, randomized crossover clinical trial with placebo as the control medication was conducted to assess psychomotor performance and subjective effects of the coadministration of MDMA and alcohol. Doses of both substances were selected in the range of those usually taken by recreational users (Gamella et al., 1997; Eckardt et al., 1998).

Materials and Methods

Subjects

The study was conducted in accordance with the Declaration of Helsinki, approved by the local Institutional Review Board (Comité Ètic d'Investigació Clínica -Institut Municipal d'Assistència Sanitària), and authorized by the Dirección General de Farmacia y Productos Sanitarios (98/112) of the Spanish Ministry of Health. All volunteers gave the written informed consent before to inclusion in the study and were paid for their participation.

Male volunteers were recruited by word of mouth. Eligibility criteria required the recreational use of MDMA on at least five occasions and previous experience in acute alcohol intoxication. Each eligible subject was initially interviewed by a physician to exclude concomitant medical conditions and psychiatric disorders, 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) to exclude individuals with history or actual major psychiatric disorders (schizophrenia, psychosis, and major affective disorder). Seventeen healthy male subjects were included in the study, eight in the pilot trial and nine in the final study. Data here presented refer to the nine volunteers who took part in the final study. They had a mean age of 23 years (range 19–36), mean body weight of 67.4 kg (range 59–81), and mean height of 175 cm (range 167–183). Their average consumption of alcohol was 1.6 units/day (1 unit = 8 g of ethanol), and referred an average of 26 previous experiences (range 5–100) with MDMA. All but two subjects were current smokers. None had a history of abuse or drug dependence according to Diagnostic and Statistical Manual of Mental Disorders IV criteria (except for nicotine dependence). None had history of adverse medical or psychiatric reactions after MDMA consumption. Subjects were phenotyped for CYP2D6 activity by using dextromethorphan as a drug probe. All participants were extensive metabolizers according to their urinary dextromethorphan/dextrorphan ratio.

Drugs

dl-MDMA was supplied by the Spanish Ministry of Health and prepared by the Department of Hospital Pharmacy of our institution as identically appearing opaque, white, soft gelatin capsules. Acute alcohol intoxication (0.8 g/kg of ethanol) was induced by the ingestion of a beverage containing vodka (Absolut, Ahus, Sweden) and tonic water (Schweppes, Madrid, Spain). Several drops of aromatic bitters and lemon juice were added to mask the placebo drink, which contained tonic water only (Farré et al., 1997). The total volume of the beverage was 350 ml. MDMA was administered in fasting state with 100 ml of tap water (two capsules each time). Volunteers began to drink the beverage 30 min after MDMA administration. The beverage was consumed in 15 min (one-third volume every 5 min).

The four drug conditions in the final study were as follows: 100 mg of *dl*-MDMA plus 0.8 g/kg of ethanol (combination condition), 100 mg of *dl*-MDMA plus placebo ethanol (MDMA condition), placebo MDMA plus 0.8 g/kg of ethanol (alcohol condition), and placebo MDMA plus placebo ethanol (placebo condition). The above-mentioned doses of MDMA and ethanol were selected according to a pilot trial in pairs of subjects ($n = 8$) where different doses of MDMA (75 and 100 mg), alcohol (0.5 and 0.8 g/kg), and their combinations were tested (Camí et al., 2000b).

Study Design

Subjects participated as outpatients in four 10-h experimental sessions with a 1-week washout period between each session. A training period of 4 to 5 h was necessary before starting study sessions to familiarize volunteers with testing procedures and questionnaires to achieve a steady performance in the digit-symbol substitution test (DSST) and the simple reaction time. The study design was double blind, double dummy, randomized crossover, and controlled with placebo. The four treatment conditions were randomly assigned using a balanced 4×4 Latin-square design. Every session day, subjects arrived at the laboratory at 8:00 AM after an overnight fast. An indwelling intravenous catheter was inserted into a subcutaneous vein in the forearm of the nondominant 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 AM (MDMA or matched placebo) and 10:00 AM (alcohol or matched placebo). A light meal was provided 3 and 6 h after MDMA administration. Tobacco smoking was permitted 6 h after drug administration. Study variables, including subjective effects, psychomotor performance, and pharmacokinetics was measured at different intervals along the session. Cardiovascular, endocrine, and other physiological parameters evaluated are not presented in this manuscript, and immunological assessment has been presented elsewhere (Pacifici et al., 2001). At each session and before drug administration, urine samples were collected to check the use of drugs of abuse (opiates, cocaine, amphetamine, and cannabis).

Study Methods

Psychomotor Performance Tests. The battery of psychomotor performance tests included the DSST, the simple reaction time, and

the Maddox-wing device. The DSST, a subtest of the Wechsler Adult Intelligence Scale-Revised designed to evaluate recognition and recording of visual information, was administered in a computerized version. Scores are based on the total number and correct responses obtained in 90 s. The simple reaction time is a measure of the sensory-motor performance and was assessed using the Vienna Reaction Unit (PC/Vienna System, Schufried, Austria). The simple reaction time is the sum of the time taken to release the control button after the light illuminated or decision time and the time taken to move the finger and depress the response button adjacent to the illuminated light or motor time. Results are expressed in milliseconds as the mean of the response time to 20 stimuli. The Maddox-wing device (Clement Clark, London, UK) measures the balance of extraocular muscles and quantifies exophoria as an indicator of extraocular muscle relaxation, and esophoria as an indicator of extraocular muscle tension. Results are expressed in diopters along the horizontal scale of the device. Details of the procedures have been previously described (Camí et al., 2000a). The DSST and the simple reaction time were performed at 0 h (immediately before MDMA administration) and at 60 and 90 min and at 2, 3, 4, 6, 8, 10, and 24 h after MDMA consumption. The Maddox-wing device was performed at 0 h (immediately before MDMA administration) and at 15, 30 (immediately before beverage), 45 (immediately after beverage), 60, 75, and 90 min and at 2, 3, 4, 6, 8, 10, and 24 h after MDMA consumption.

Subjective Effects Rating Scales. Subjective effects were measured using the 49-item short form of the Addiction Research Center Inventory (ARCI) and a set of 23 different visual analog scales (VASs). ARCI is a true-false questionnaire constructed to evaluate subjective effects of psychoactive drugs, which was administered in a Spanish-validated version (Lamas et al., 1994; Arasteh et al., 1999). The questionnaire includes five scales: pentobarbital-chlorpromazine-alcohol group (PCAG), a measure of sedation; morphine-benzedrine group (MBG), a measure of euphoria; lysergic acid diethylamine group (LSD), a measure of dysphoria and somatic symptoms; benzedrine group (BG), a stimulant scale consisting mainly of items relating to intellectual efficiency and energy; and amphetamine (A), an empirically derived scale sensitive to the effects of *d*-amphetamine. ARCI was administered at 0 h (immediately before MDMA consumption) and at 15, 30, 45, 60, and 90 min and at 2, 3, 4, 6, 8, 10, and 24 h after MDMA administration.

A total of 23 visual analog scales (100 mm) labeled with different adjectives marked at opposite ends with "not at all" and "extremely" were used (Camí et al., 2000a). Subjects rated effects of "stimulated", "high", "drunken", "any effect", "good effects", "bad effects", "liking", "content", "drowsiness", "changes in distances", "changes in colors", "changes in shapes", "changes in lights", "hallucinations-seeing 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". These scales allow the evaluation of subjective feelings of euphoria, stimulant and sedative effects, changes in sensory perceptions, presence of hallucinations, changes in body perceptions, and physical effects. Scales were administered at 0 h (immediately before MDMA administration) and at 15, 30, 45, 60, and 90 min and at 2, 3, 4, 6, 8, 10, and 24 h after MDMA use.

Analytical Assays. Blood was collected at each session to preserve the double blind masking of the study. Blood samples (5 ml, heparinized tubes) were obtained for analysis of MDMA at 0, 15, 30, 45, 60, 75, and 90 min and at 2, 3, 4, 6, 8, and 10 h after MDMA administration. Samples were processed together with a calibration curve. MDMA-D_5 was used as MDMA internal standard. One milliliter of plasma was required for analysis and pH was adjusted to 5 by adding 1 ml of 1.1 M acetate buffer, pH 5.2. Fishman units (20,000) of β-glucuronidase (50 μl) were added to each sample and incubation was done for 16 h at 37°C. Samples were processed by an extraction and derivatization method previously published (Mas et al., 1999; Ortuño et al., 1999). Solid-liquid extraction with Bond Elut Certify columns (Varian, Harbor City, CA) was performed and elution was done with 2 ml of ethyl acetate (2% of ammonium hydroxide). Trifluoroacyl derivatives were formed by reaction with 50 μl of *N*-methyl-bis(trifluoroacetamide) as derivatization agent. A gas chromatograph (HP 6890 series GC system; Hewlett Packard, Palo Alto, CA) equipped with a quadrupole mass spectrometer (HP 5973 mass selective detector) and an autosampler (HP 5683 series injector) was used. Separation was done using a cross-linked 5% phenylmethylsiloxane capillary column (12 m × 0.2 mm i.d. × 0.3-μm film thickness) (Ultra-2; Hewlett Packard). The mass spectrometer was operated by electron impact ionization (70 eV) and in the selected ion monitoring acquisition mode. Ions were selected for each substance. Those selected to quantify MDMA were m/z = 154 for MDMA and m/z = 158 for MDMA-D_5. Calibration curves for the GC-MS methods were linear over 25 to 400 ng/ml (plasma) concentration ranges for MDMA. Limit of quantification was lower than 19.1 ng/ml for MDMA. Interday precision and accuracy values were lower than 10.1 and 6.1%, respectively, for compounds analyzed.

Blood samples (2 ml) were also obtained for analysis of ethanol at 0, 15, 30, 45, 60, 75, and 90 min and at 2, 3, 4, and 6 h after MDMA administration (or −30, −15, 0, 15, 30, 45, 60, 90 min and at 2.50, 3.50, and 5.50 h after starting beverage administration). Ethanol determination in total blood was performed using a validated method previously published (Farré et al., 1993). Blood (1 ml) was added to an 8-ml vial containing 1 ml of Milli-Q water and 243 ng of *n*-butanol as internal standard. A gas chromatograph (HP 5890; Hewlett Packard) fitted with a headspace injector HP 19395A and equipped with a flame ionization detector was used for ethanol quantification in blood and urine. Analyses were performed in a cross-linked polyethylene glycol capillary column (15 m × 0.33 mm × 1 μm) (HP-INNOWax; Hewlett Packard).

Statistical Analysis

Values from psychomotor performance measures and subjective variables were transformed to differences from baseline. The peak effect in the first 6 h (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 for each variable. These transformations were analyzed by one-way repeated measure analysis of variance (ANOVA) with drug conditions as factor. When ANOVA results showed significant differences between treatment conditions, 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 two-way ANOVA with treatment condition and time (0–10 h) as factors. When treatment condition or the treatment condition × time interaction was statistically significant, multiple Tukey's post hoc comparisons were performed at each point of time using the mean square error term of the treatment condition × time interaction. With regard to plasma concentrations of MDMA and ethanol, the following parameters were calculated: peak concentration (C_{max}), time taken to reach peak concentration (T_{max}), and area under the concentration-time curve from 0 to 6 or 0 to 24 h ($AUC_{0-6\ h}$ for alcohol; $AUC_{0-24\ h}$ for MDMA). AUC values were calculated by the trapezoidal rule. 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

Psychomotor Performance. Results of psychomotor performance tests after administration of drug conditions are shown in Table 1 and Fig. 1. In the DSST task, the two conditions including alcohol produced a significant decrease in the number of total and correct responses compared with placebo and MDMA. In the $AUC_{0-6\ h}$ analysis, the combina-

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TABLE 1
Significant statistical results of psychomotor performance and subjective evaluations

Variable		ANOVA (df = 3,24)		Tukey's Multiple Comparison Test					
				Placebo			MDMA		Alcohol
		F	p Value	Alcohol	MDMA	MDMA-OH	Alcohol	MDMA-OH	MDMA-OH
Psychomotor performance									
DSST total	AUC	5.554	0.005	**	N.S.	N.S.	*	N.S.	N.S.
	Peak	8.316	0.001	**	N.S.	**	*	N.S.	N.S.
DSST correct	AUC	8.807	<0.001	**	N.S.	N.S.	**	N.S.	N.S.
	Peak	10.070	<0.001	**	N.S.	**	**	**	N.S.
RT decision	AUC	3.019	0.050						
	Peak	3.743	0.024	N.S.	N.S.	*	N.S.	N.S.	N.S.
Maddox-wing	AUC	13.024	<0.001	N.S.	**	N.S.	**	N.S.	**
	Peak	15.208	<0.001	N.S.	**	N.S.	**	N.S.	**
ARCI questionnaire									
PCAG	AUC	8.590	<0.001	*	N.S.	N.S.	**	N.S.	**
	Peak	6.400	0.002	*	N.S.	N.S.	**	N.S.	*
MBG	AUC	12.911	<0.001	N.S.	**	**	*	N.S.	**
	Peak	16.530	<0.001	N.S.	**	**	*	N.S.	*
LSD	AUC	5.716	0.004	N.S.	**	*	N.S.	N.S.	N.S.
	Peak	4.538	0.012	N.S.	*	*	N.S.	N.S.	N.S.
BG	AUC	7.151	0.001	N.S.	N.S.	*	N.S.	N.S.	**
	Peak	6.289	0.003	N.S.	N.S.	*	*	N.S.	*
A	AUC	14.101	<0.001	N.S.	**	**	*	N.S.	**
	Peak	27.629	<0.001	**	**	**	**	N.S.	**
Visual analog scales									
Stimulated	AUC	22.790	<0.001	N.S.	**	**	**	N.S.	**
	Peak	30.335	<0.001	N.S.	**	**	**	N.S.	**
High	AUC	22.246	<0.001	N.S.	**	**	**	N.S.	**
	Peak	21.832	<0.001	N.S.	**	**	**	N.S.	**
Drunken	AUC	11.952	<0.001	**	N.S.	**	**	**	N.S.
	Peak	26.882	<0.001	**	N.S.	**	**	**	N.S.
Any effect	AUC	21.088	<0.001	*	**	**	N.S.	N.S.	**
	Peak	29.192	<0.001	**	**	**	*	N.S.	**
Good effects	AUC	27.270	<0.001	N.S.	**	**	N.S.	*	**
	Peak	33.009	<0.001	**	**	**	**	N.S.	**
Liking	AUC	16.598	<0.001	N.S.	**	**	N.S.	*	**
	Peak	19.653	<0.001	**	**	**	*	N.S.	*
Content	AUC	20.139	<0.001	N.S.	**	**	N.S.	*	**
	Peak	15.625	<0.001	**	**	**	N.S.	N.S.	N.S.
Drowsiness	AUC	8.409	0.001	**	N.S.	N.S.	**	N.S.	**
	Peak	6.360	0.003	**	N.S.	N.S.	*	N.S.	*
Changes in colors	AUC	1.606	0.214						
	Peak	3.601	0.028	N.S.	*	N.S.	N.S.	N.S.	N.S.
Changes in shapes	AUC	3.467	0.032	N.S.	N.S.	*	N.S.	N.S.	N.S.
	Peak	3.090	0.046	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Changes in lights	AUC	4.914	0.008	N.S.	*	N.S.	N.S.	N.S.	N.S.
	Peak	8.377	0.001	N.S.	**	*	**	N.S.	N.S.
Confusion	AUC	5.104	0.007	N.S.	*	N.S.	*	*	N.S.
	Peak	4.989	0.008	N.S.	*	N.S.	*	*	N.S.
Different body feeling	AUC	14.751	<0.001	N.S.	**	**	*	N.S.	**
	Peak	14.996	<0.001	N.S.	**	**	**	N.S.	**
Different surroundings	AUC	3.170	0.043	N.S.	N.S.	*	N.S.	N.S.	N.S.
	Peak	4.292	0.015	N.S.	*	*	N.S.	N.S.	N.S.

MDMA-OH, MDMA and alcohol combination. Tukey's test N.S., not significant.
* $p < 0.05$; ** $p < 0.01$: blank, not done (ANOVA not significant).

tion condition obtained lower values in comparison with alcohol, but the difference was not significant. Peak effects appeared at similar times in both alcohol conditions (90 min after MDMA administration or 60 min after beverage). The mean peak differences between alcohol and placebo were −5.89 total and −9.0 correct responses, and between drug combination and placebo were −4.89 total and −8.11 correct responses. The mean peak differences between alcohol and MDMA alone conditions were −4.78 total and −8.11 correct responses, and between combination and MDMA were −8.11 correct responses. In the time course of effects, the impairment produced by alcohol in the DSST lasted longer than those induced by the combination. Alcohol impaired DSST significantly in comparison with placebo during 2 to 3 h (from 1 h to 3–4 h after administration). For the combination the impairment in the DSST was significant in comparison with placebo during 1 h (1–2 h after administration).

In comparison with placebo the drug combination increased the decision time at peak effects. In the time course profile, both alcohol and combination increased the total reaction time and the decision time in comparison with placebo at different time points (Fig. 1). No differences were observed between both conditions that included alcohol but impairment was greater under the combination. The impairment induced by the drug combination had a half-hour duration between 1 and 1.5 h after MDMA administration.

In the Maddox-wing device, MDMA produced a statistical significant increase in the degree of esophoria compared with placebo and alcohol ($AUC_{0-6\ h}$ and peak effects). Moreover, alcohol slightly increased exophoria, but no significant dif-

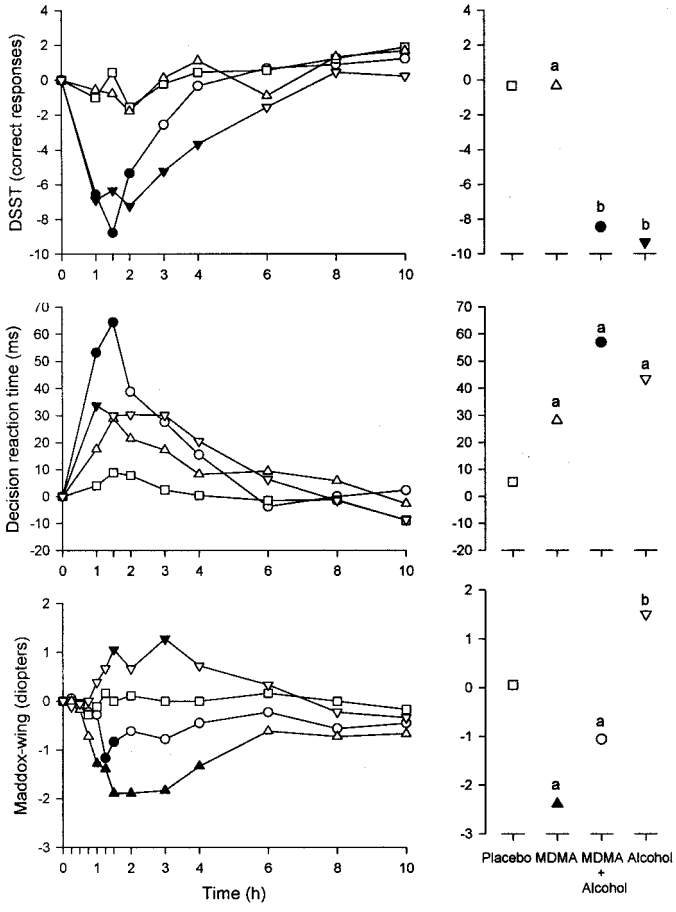

Fig. 1. Time course of drug effects (left) and peak drug effects (right) on psychomotor performance (differences from baseline). Data points represent means from nine subjects. Filled symbols indicate a significant difference from placebo ($p < 0.05$). Letters a and b indicate comparisons among the three active conditions; within the same panel, any two means designated with the same letter are not significantly different from each other at $p < 0.05$ (Tukey's post hoc test). □, placebo; △, MDMA (100 mg); ○, MDMA (100 mg) + alcohol (0.8 g/kg); ▽, alcohol (0.8 g/kg).

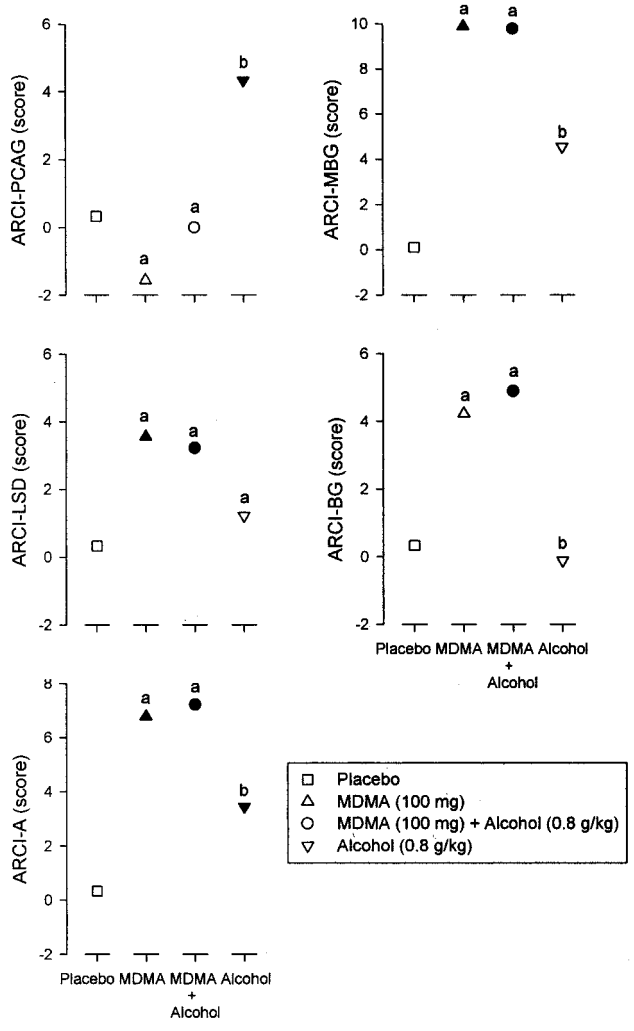

Fig. 2. Peak drug effects on ARCI questionnaire (differences from baseline). Data points represent means from nine subjects. Filled symbols indicate a significant difference from placebo ($p < 0.05$). Letters a and b indicate comparisons among the three active conditions; within the same panel, any two means designated with the same letter are not significantly different from each other at $p < 0.05$ (Tukey's post hoc test).

ferences were obtained compared with placebo. The drug combination scored in the middle of alcohol and MDMA conditions. As show in Fig. 1, the combination reversed in part the exophoria induced by alcohol ($AUC_{0-6\,h}$ and peak effects) and attenuated the esophoria produced by MDMA. Along the time course, MDMA induced a significant esophoria during 3 h (from 1–4 h) in comparison with placebo, but in the combination condition esophoria was lower and only lasted 15 min (1.15–1.30 h). Alcohol produced a significant exophoria at two time points (1.5 and 3 h) in comparison with placebo.

Subjective effects results are shown in Table 1 and Figs. 2 to 4. In general terms, subjective effects reached their maximum between 1 and 2 h and returned to basal values 4 h after drug administration. In the ARCI questionnaire (Figs. 2 and 4), alcohol produced a statistically significant increase in scores of the PCAG (sedation) scale in comparison with all other conditions. MDMA administration completely reversed the effects of alcohol on PCAG, indicating a reduction in sedation. The drug combination produced similar scores than MDMA alone in this scale. Alcohol-induced sedation peaked at 2 h (1.25 h after beverage) and remained significant in the time course analysis during 2 h (2–4 h).

Both conditions including MDMA produced an increase in euphoria scores (MBG scale) in comparison with placebo and alcohol. This effect was particularly evident at 90 min. The MBG peak difference scores were 9.78 and 9.67, when MDMA and drug combination were compared with placebo, and 5.33 and 5.22 when they were compared with alcohol. With regard to the time course, in comparison with placebo, the euphoric effects produced by alcohol, MDMA, and combination lasted 15 min, 2.25 h, and 5.25 h, respectively. The combination induced similar maximal effects but longer duration of the euphoria. Both conditions including MDMA increased LSD (dysphoria) scores compared with placebo. No differences were observed with alcohol. The effects were slightly higher under MDMA and peaked at 1 h. Drug combination and MDMA increased BG scores, a scale related to intellectual efficiency and energy, in comparison with placebo and alcohol, but alcohol decreased the scores in comparison with placebo (not significant). The combination induced higher scores and longer duration of effects than MDMA alone. The ethanol effects in this scale were reverted com-

pletely by MDMA administration. As observed in the MBG scale, the maximal effect was observed at 90 min.

All active conditions produced an increase in the A scale scores, a scale derived from items of MBG and BG scales, compared with placebo. Compared with alcohol, both drug combination and MDMA induced higher scores (AUC and peak effects). With regard to the time course, all three active conditions were different from placebo at 45 min, but the duration of these differences was shorter with alcohol (45 min) and longer with MDMA (3.25 h) and the combination (5.25 h).

In reference to the 23 VAS administered during the study (Table 1; Figs. 3 and 4), all active conditions increased the scores of the VAS any effect, good effects, liking, and content in comparison with placebo. Both MDMA and combination increased the scores of the VAS stimulated; high; changes in lights; different, changed or unreal body feeling; and different or unreal surroundings in comparison with placebo. Both alcohol and combination increased scores of VAS drunken in comparison with placebo or MDMA. The combination induced higher scores than MDMA in VAS good effects, liking, content, and drunken, but MDMA scored higher in VAS confusion in comparison with the combination. In comparison with alcohol, the drug combination increased the scores

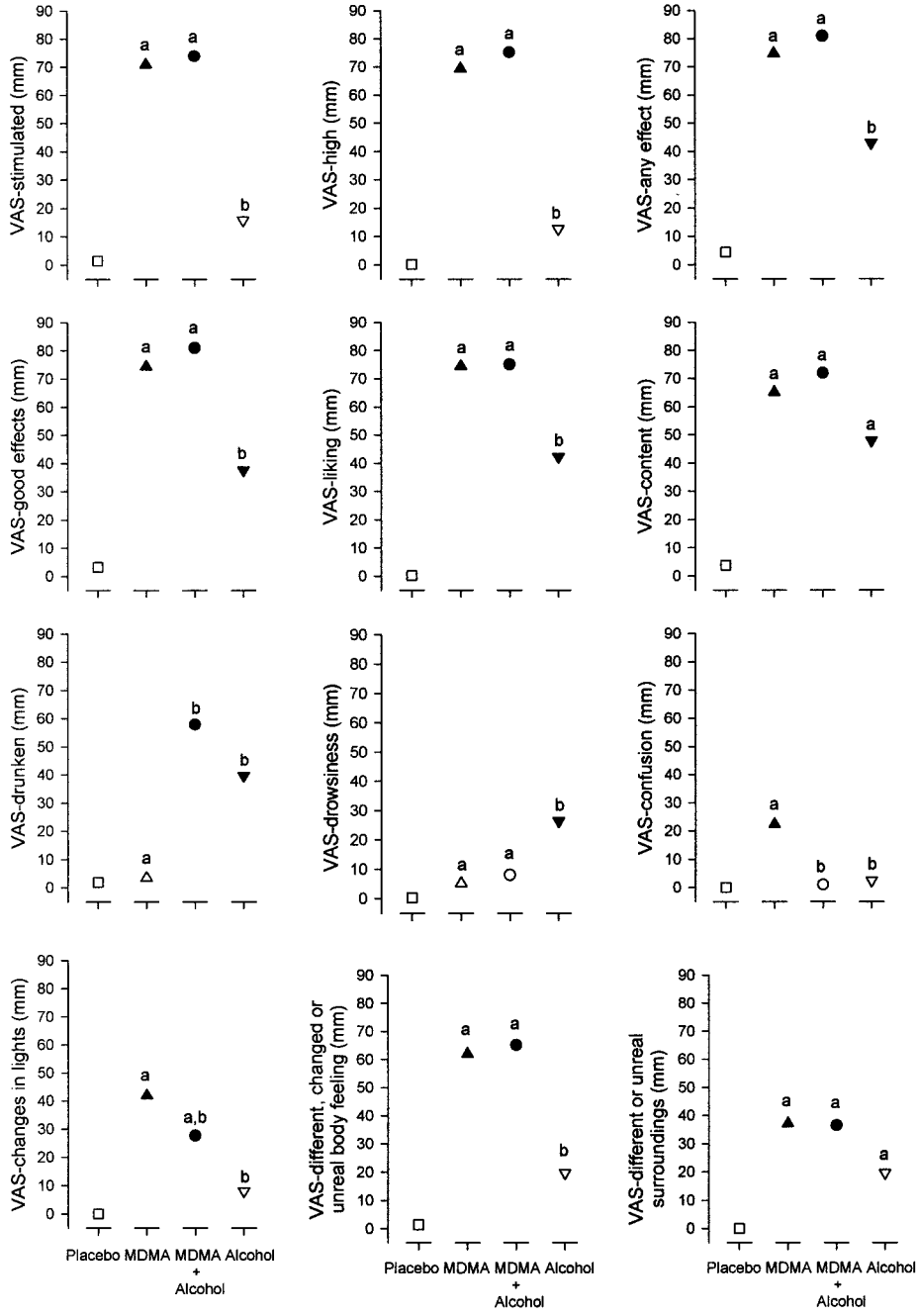

Fig. 3. Peak drug effects on VAS (differences from baseline). Data points represent means from nine subjects. Filled symbols indicate a significant difference from placebo ($p < 0.05$). Letters a and b indicate comparisons among the three active conditions; within the same panel, any two means designated with the same letter are not significantly different from each other at $p < 0.05$ (Tukey's post hoc test). □, placebo; △, MDMA (100 mg); ○, MDMA (100 mg) + alcohol (0.8 g/kg); ▽, alcohol (0.8 g/kg).

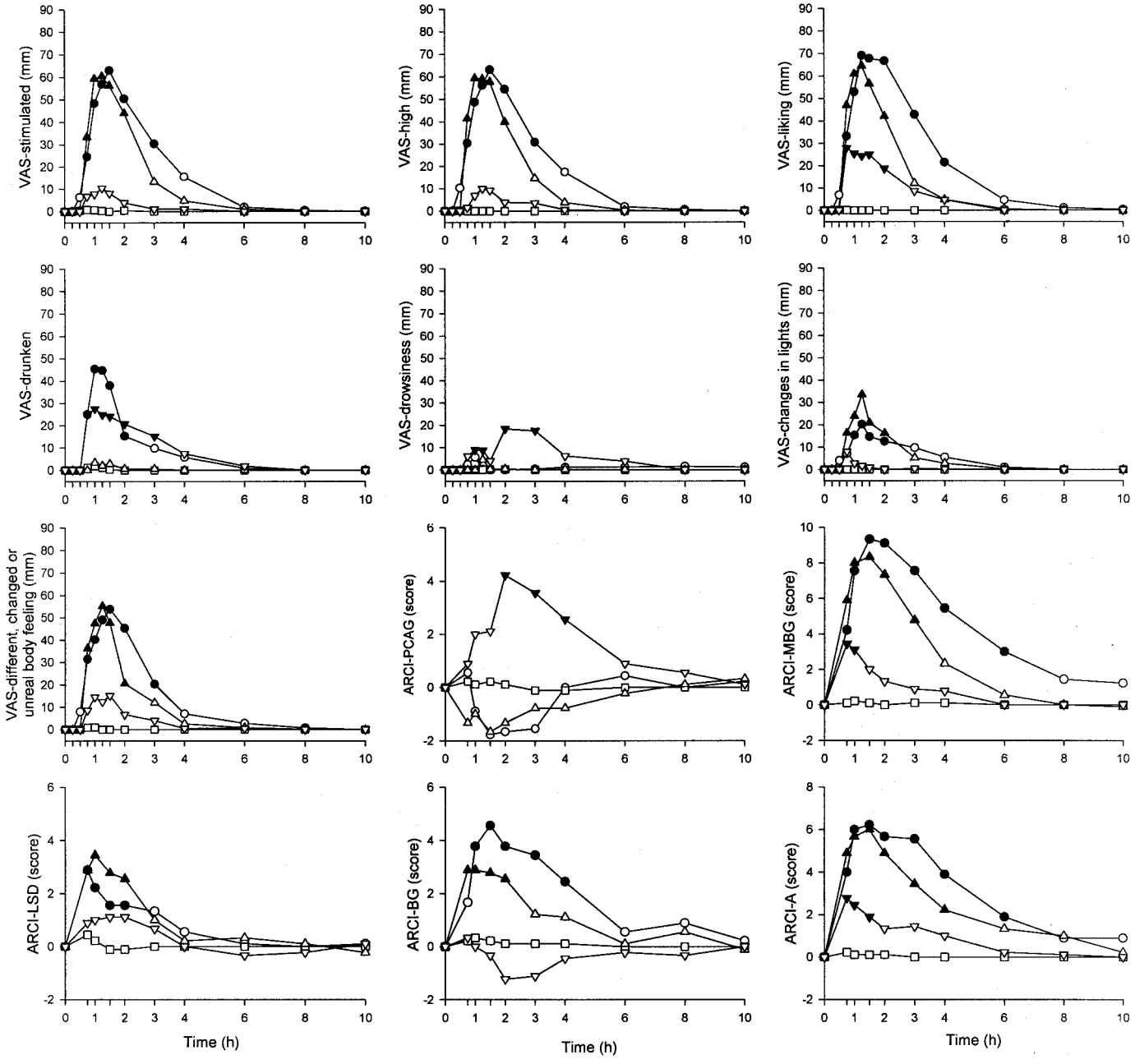

Fig. 4. Time course of drug effects on VAS and ARCI questionnaire (differences from baseline). Data points represent means from nine subjects. Filled symbols indicate a significant difference from placebo ($p < 0.05$). □, placebo; △, MDMA (100 mg); ○, MDMA (100 mg) + alcohol (0.8 g/kg); ▽, alcohol (0.8 g/kg).

in VAS stimulated; high; any effect; good effects; liking; content; and different, changed or unreal body feeling. MDMA decreased the VAS drowsiness induced by alcohol, but did not induced significant changes in the VAS drunken. None drug condition induced changes in VAS related to hallucinations. In reference to the time course effects of VAS scores (Fig. 4), the drug combination increased the duration of the effect in reference to MDMA alone in approximately 1 to 2 h, but in general the peak intensity of these effects were similar.

No serious adverse reactions were observed. None of the participants required specific therapy or special care during the experimental sessions and all of them finalized the study.

The administration of alcohol increased the C_{max} of MDMA in comparison with when only MDMA was administered. This increase represents a 13% higher concentration of MDMA (Table 2). No differences were found in T_{max} or $AUC_{0-24\ h}$ between both conditions. The administration of MDMA reduced the plasma levels of ethanol compared with the alcohol alone condition. The changes were significant on $AUC_{0-6\ h}$ and C_{max} (Table 2), with a mean decrease of 9 and 15%, respectively. The T_{max} was delayed in the drug combination, with a median of 30 min.

Discussion

To our knowledge, results of this study provide the first information in humans about the pharmacodynamics (psychomotor performance and subjective effects) and pharmaco-

TABLE 2
Pharmacokinetic parameters for alcohol and MDMA [n = 9, values are mean ± S.D. except for T_{max} (median)]

Drug	Condition	C_{max}	T_{max}	$AUC_{0-6\ h}$
		mg/dl	*h*	*mg/dl·h*$^{-1}$
Alcohol	Alcohol	124.62 ± 14.94	1.5	409.08 ± 24.28
	MDMA + Alcohol	105.81 ± 4.99	2	371.74 ± 18.67
	p value	0.004	0.014	<0.001
MDMA	MDMA	231.42 ± 36.20	1.5	2447.85 ± 711.81
	MDMA + Alcohol	260.29 ± 42.22	1.5	2345.08 ± 838.35
	p value	0.007	0.058	0.471

kinetics of MDMA and alcohol interactions. The administration of 100 mg of MDMA, a dose in the range of doses used recreationally (Gamella et al., 1997), produced subjective effects similar to own observations in a previous study in which 75 and 125 mg were used (Camí et al., 2000a). Similar feelings of euphoria, stimulation, and perception changes have been found by other studies (Grob et al., 1996; Vollenweider et al., 1998). In our study, neither hallucinations nor psychotic reactions were observed, although these effects were reported after the administration of 3,4-methylenedioxyethamphetamine to healthy subjects (Hermle et al., 1993). In reference to the psychomotor performance tests, MDMA did not induce any change in DSST and reaction time compared with placebo.

The alcohol dose (0.8 g/kg) used in this study produced the expected effects in subjective and performance parameters. Alcohol increased drunkenness feeling, produced significant changes in some euphoric-related effects, and augmented sedation. Alcohol impaired psychomotor performance increasing the simple reaction time and diminishing the number of total and correct responses in DSST. These results are in agreement with observations made in other studies using similar methods of evaluation and a wide range of alcohol doses (0.5–1 g/kg) (Kerr et al., 1991; Farré et al., 1993; Eckardt et al., 1998; Kerr and Hindmarch, 1998). In this study alcohol induced euphoric- and sedative-like subjective effects during the ascending slope of the alcohol dose-response curve, but only sedative-like effects during the descending slope, as described in previous observations (Holdstock and de Wit, 1998).

The drug combination mainly produced a profile of effects similar to MDMA. The combination of MDMA and alcohol induced stimulant and euphoric effects as demonstrated by important increases of ARCI-MBG, ARCI-BG, ARCI-A, and VAS stimulated, high, good effects, or liking scores. The addition of alcohol to MDMA did not increase the maximal effects on these measures but prolonged its duration, increasing its total magnitude. The increase in the ARCI-MBG, a clear measure of drug-induced euphoria, are in the range of our previous study and reach scores as high as induced by other drugs with a well known abuse potential (e.g., cocaine or amphetamine) (Arasteh et al., 1999). In reference to the alcohol intoxication, MDMA did not change the drunkenness induced by alcohol, but reduced some of its sedative actions. In our study, like others (Holdstock and de Wit, 1999), alcohol alone induced an increase in the ARCI-PCAG scores as an indication of drug-induced sedation. MDMA administration antagonized the effects of alcohol on ARCI-PCAG and VAS drowsiness, indicating a reduction in the subjective feeling of sedation. On the other hand, MDMA also reverted the effects of alcohol on the ARCI-BG, increasing the scores above those obtained after MDMA alone administration. This scale is a recognized measure of intellectual efficiency, and the administration of amphetamines or other stimulants increases the scores (Camí et al., 2000a), whereas the administration of sedatives as benzodiazepines or alcohol decrease the scores (Farré et al., 1996, 1997; Holdstock and de Wit, 1999).

Taking into account the results of the psychomotor performance tasks, which can be considered an objective measure of intellectual efficiency and sedation, the administration of the combination induced a similar impairment to that of alcohol alone in the scores of the DSST, but increased slightly the decision component of reaction time in comparison with alcohol alone. Although the results seem relevant for road safety, as occur with laboratory-based tasks, its extrapolation in terms of driving performance is limited.

MDMA administration reverted, in part, the exophoria induced by alcohol in the Maddox-wing test. This task is a direct measure of the extraocular musculature relaxation and indirect measure of central sedation. The administration of sedatives such as benzodiazepines or ethanol induced exophoria (Farré et al., 1993, 1996), whereas the administration of stimulants as amphetamine or MDMA produced esophoria (Camí et al., 2000a). These findings suggest that MDMA can reduce the sedation associated to alcohol administration. Other stimulants such as caffeine were able to counteract the exophoria and sedation induced by two hypnotics, triazolam and zopiclone (Mattila et al., 1992). In contrast, cocaine did not attenuate the exophoria induced by alcohol, probably because cocaine by itself does not produce changes in heterophoria (Farré et al., 1993). Interestingly, the maximal impairment on psychomotor performance and the maximal euphoric and stimulants effects peaked at 90 min after MDMA-alcohol combination (1 h after alcohol consumption), whereas sedative effects peaked at 2 h after MDMA administration (1.5 h after alcohol intake).

It seems that alcohol is able to slightly increase the plasma levels of MDMA, and MDMA reduced the ethanol plasma levels. The mechanism for the increase in MDMA plasma concentrations by ethanol is unknown. For dextroamphetamine an increase in bioavailability has been proposed (Perez-Reyes et al., 1992), others suggested a reduction in the metabolism of methamphetamine and amphetamine (Shimosato, 1988) but Mendelson et al. (1995) did not find differences in plasma concentrations of methamphetamine. The decrease in ethanol concentrations observed after MDMA administration was consistent with findings of a previous study in which alcohol and cocaine were coadministered (Farré et al., 1993, 1997). The mechanism of this interaction could be related to changes in ethanol absorption or initial distribution. The changes observed in the kinetics of MDMA and ethanol, although significant in statistical terms, are mild in magnitude and could be considered in the range of the interindividual variability. These pharmacokinetic changes may account, in part, for the effects observed, although a pharmacodynamic interaction might also be possible. Regarding the neurotoxic effects of MDMA in humans, the increase in MDMA plasma levels might have clinical significance taking into account that these substances are commonly coadministered.

Overall, it seems that MDMA reduced the subjective feelings of sedation induced by alcohol but the drug did not

reverse alcohol-induced impairment of psychomotor performance. This dissociation between subjective and objective sedation is of interest. Although subjects may feel less or not sedated by alcohol and have the feeling of performing more efficiently, psychomotor abilities remain impaired or unchanged. The potential impact of this dissociation in terms of road safety is unknown, but it may be plausible that subjects would consider they are driving better when actual performance continues to be impaired by the effect of alcohol. We could speculate that MDMA-alcohol combined use may potentiate the bizarre and reckless behavior among drivers as other studies have pointed out (Hooft and van de Voorde, 1994). This dangerous behavior may result from the euphoria, stimulation, and antisedative effects of drug combination, which were not corroborated by a better psychomotor performance.

In summary, MDMA reversed the subjective sedation induced by alcohol but did not reduce drunkenness feelings. MDMA did not reverse the actions of alcohol on psychomotor abilities. The MDMA-alcohol combination induced longer lasting euphoria and well being than MDMA or alcohol alone; therefore, the combination of MDMA and alcohol could have an increased abuse potential than MDMA alone. The extrapolation of our results in terms of road safety could be relevant if confirmed by field epidemiological studies and experimental studies in real driving conditions by using different doses of both compounds.

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