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ORIGINAL INVESTIGATION

MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function

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Abstract
Rationale The party drug ecstasy is frequently used in combination with other drugs like marihuana and alcohol. In addition, a substantial proportion of the MDMA users has claimed to drive a car when under the influence of MDMA and/or other drugs.
Objective To assess the effects of MDMA and alcohol, combined and alone, on actual driving performance and laboratory tasks related to driving.
Methods Eighteen healthy subjects participated in a double-blind, placebo-controlled, six-way cross-over study. Treatments consisted of MDMA 0, 75, and 100 mg with and without alcohol, aiming at 0.06 mg/ml BAC. Laboratory tests (critical tracking task, object movement estimation task) were conducted between 1.5 and 2 h postdrug (0.5 and 1 h postalcohol). Actual driving tests (road tracking test, car-following test) were conducted between 3 and 5 h postdrug (2 and 4 h postalcohol). Subjects completed the addiction research center inventory (ARCI) and rated their driving quality and mental effort during driving.
Results Alcohol alone impaired critical tracking performance, as well as a number of actual driving performance parameters [i.e., standard deviation of lateral position (SDLP), brake reaction time, and coherence]. MDMA alone reduced SDLP and standard deviation of speed. MDMA significantly moderated alcohol induced impairment of road tracking performance but did not affect alcohol impairments of car-following and laboratory task performance. Subjective data seemed to support objective data.
Conclusion MDMA moderated the impairing effects of a low dose of alcohol on road tracking performance but it could not overcome alcohol-induced impairment on other aspects of driving behavior or driving related performance.

Keywords Actual driving performance · MDMA · Alcohol

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Introduction

The party drug ecstasy (3,4 methylenedioxymethamphetamine, MDMA) is frequently used in combination with other drugs (Topp et al. 1999; Riley et al. 2001; Logan and Couper 2001; Barrett et al. 2005). Attendees at raves or dance parties have attested to the use of one (2.7%) or more substances (80%) during rave parties (Barrett et al. 2005). In half of the cases, MDMA was generally used in combination (92.3%) with substances like cannabis (68.5%), amphetamine (48.4%), and/ or alcohol (45.2%). Furthermore, when questioning rave attendees whether they would drive while using drugs, the conclusion was that up to 36% drove after having taken drugs (Riley et al. 2001). Several fatal and nonfatal road accidents have been reported in which MDMA was found in the plasma of drivers, alone or in combination with other drugs or alcohol (Logan and Couper 2001; Carmen del Rio et al. 2002). In addition, a few case reports have described erratic driving behaviors in drivers under the influence of MDMA. These behaviors included ignoring traffic signs and traffic lights and speeding (Schifano 1995; Henry et al. 1992).

Experimental studies of the acute effects of MDMA on psychomotor performance and actual driving behavior have shown that certain aspects like tracking in a compensatory tracking task and weaving in an on-the-road driving task improved after a single dose, whereas other aspects like time to contact estimation in a dual attention task and gain, a parameter modeling speed adaptations in an on-the-road car following task, deteriorated (Lamers et al. 2003; Ramaekers et al. 2006, in press). The improvement of certain aspects of actual driving performance seems to be mediated by manipulations of the dopaminergic system as similar driving improvement was noted for the dopaminergic agent methylphenidate. The impairment of more complex, controlled behavior as measured by the car-following task seems to be due to actions on the serotonergic system as methylphenidate did not affect this behavior whereas MDMA did (Ramaekers et al. 2006, in press).

Up till now, only two studies investigated the effects of a MDMA-alcohol combination on performance, in a controlled experimental setting (Hernandez-Lopez et al. 2002; Ramaekers and Kuypers 2006). Hernandez-Lopez et al. (2002) reported a discrepancy between subjective measures of sedation and objective measures of psychomotor impairment. MDMA moderated the subjective experience of alcohol-induced sedation, but it did not compensate for the alcohol-induced impairments on objective measures of psychomotor performance. Ramaekers and Kuypers (2006) found that increments in motor impulsivity caused by alcohol were not reduced by simultaneous administration of MDMA. Overall, these two studies seem to indicate that the stimulant effect of MDMA was not sufficient to compensate for the impairing effects of alcohol on psychomotor function and impulse control.

Brookhuis et al. (2004) conducted a quasicontrolled, naturalistic study to assess driving performance of MDMA users in an advanced driving simulator before and after visiting a rave party. All subjects indicated that they had taken MDMA (average dose: 56 mg) just before going to the party and 30–40% of them also attested to the concomitant use of alcohol and/or marijuana. When returning from the party, most of the subjects had taken additional doses of MDMA (70%), marijuana (80%), or alcohol (90%). The participants were also tested sober, at a comparable time as the first MDMA ride. The results indicated that driving performance was not greatly affected before the rave party, but deteriorated during the night after multiple drug use. The most striking result was the apparent decreased sense for risk taking as shown for example by the acceptance of smaller gaps between cars. This data suggest that combined use of MDMA and alcohol or marijuana produces more severe driving impairment than MDMA alone. However, it should be noted that these data are also confounded by time of testing. Driving impairment was primarily observed when subjects had build up a full night of sleep loss, at the end of the rave. It can thus not be excluded that exhaustion by itself may also have played a major role in driver impairment observed after multiple drugs use.

The aim of the present study was primarily to assess the acute effects of a single dose of MDMA (75 or 100 mg) with and without a low dose of alcohol on actual driving performance in MDMA users in a double blind, placebo-controlled, crossover design. Two psychomotor tasks were incorporated in the study to assess driving related behavior, i.e., tracking and time to contact. Two actual driving tests were included to assess different aspects of driving performance like automated behavior and driving at the tactical level, in the road tracking task and car-following task, respectively. Four subjective questionnaires were added to assess driving quality, mental effort, and drug-induced effects. The primary question was whether the combined effects reduced or increased actual driving performance and driving-related behavior.

Materials and methods

Design and treatments

The study design was double-blind, placebo-controlled, 6-way cross-over with balancing of the treatment orders. Orders were arranged according to three Latin squares and this resulted in six treatment orders which were randomly assigned to 18 subjects. The treatments consisted of MDMA 0, 75, and 100 mg with and without alcohol. MDMA and MDMA placebo were administered orally in identically appearing formulations. MDMA was administered as a 25-ml solution in bitter orange peel syrup, which was ingested at once. Alcohol dosing was designed to produce a peak blood alcohol concentration (BAC) of about 0.06 mg/ml during laboratory testing and a concentration that was under the legal limit for driving (0.05 mg/ml) during driving tests. Alcohol doses were administered at 45 min postdrug and consumed within a period of 15 min. Before driving tests took place, subjects were given an additional dose of alcohol to keep their BAC levels approximately constant during the tests.

The doses of MDMA administered in this study were selected in the range of the commonly used doses that is 50 to 150 mg (Henry 1992; Parrott 2004). Because the pharmacokinetics of MDMA appears to be nonlinear, we selected 75 mg MDMA as our lowest dose and 100 mg as our highest dose. A small increase in dose from 75 to 100 mg was expected to approximately double MDMA concentrations in blood (de la Torre et al. 2004).

Laboratory tests were conducted between 1.5 and 2 h postdrug (0.5 and 1 h postalcohol) and driving tests took place between 3 and 5 h postdrug (2 and 4 h postalcohol).

Participants

Eighteen recreational MDMA-users, nine men and nine women, were recruited through poster advertisements at Maastricht University and advertisements in local newspapers. Initial screening was based on a questionnaire on medical history and driving experience. Subjects who were accepted were examined by the medical supervisor, who also checked vitals signs and took blood and urine samples. Standard blood chemistry, hematological and drug screen tests were conducted on these samples. Inclusion criteria were experience with the use of MDMA; free from psychotropic medication; good physical health as determined by examination and laboratory analysis; absence of any major medical, endocrine, and neurological condition; normal weight, body mass index (weight/height^2) between 18 and 28 kg/m^2; and possession of a valid driving license and written informed consent. Exclusion criteria were history of drug abuse (other than the use of MDMA) or addiction; pregnancy or lactation; cardiovascular abnormalities as assessed by standard 12-lead ECG; excessive drinking (>20 standard alcoholic consumptions a week); hypertension (diastolic—100; systolic—70); and history of psychiatric or neurological disorder.

Characteristics Subjects had a mean (SD) age of 26.6 (5.4) and a mean (SD) weight of 70.39 (17.9). They drove on average (SD) 18,444.44 (13,536.3) kilometer per year, and were all light to moderate users of MDMA who reported to have taken the drug on 2–25 occasions (mean: nine occasions) in the previous year. Overall, subjects reported to have taken between 2–120 MDMA tablets (mean: 18 tablets) in the previous year. Seventy-two percent of them admitted they had ever driven a car under the influence of MDMA of whom 83% had also done it in combination with alcohol.

This study was conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Edinburgh (2000). All subjects gave their informed consent, in writing. Approval for the study was obtained from the University's Medical Ethics committee. A permit for obtaining, storing and administering MDMA was obtained from the Dutch drug enforcement administration. Subjects were paid for their participation in the study.

Study procedure

Subjects were asked to refrain from any drugs starting 1 week before the medical screening and physical examination until 2 weeks after the last experimental session. The subjects were not allowed to use alcohol or caffeinated beverages on the day before an experimental session and were requested to arrive at experimental sessions well rested. Drug screens in urine and alcohol screens in breath were performed before experimental sessions upon arrival of the subject. Subjects who tested positive on alcohol or drugs screens were sent home and scheduled to return to the laboratory at a later time. Subjects were transported from their homes to the laboratory or vice versa by one of the experimenters to prevent subjects from driving while intoxicated on the day of testing. Additional clinical blood chemistry, with particular reference to liver and renal function was conducted at day 7 after each treatment. All subjects received a training session before onset of the experimental sessions to familiarize them with the tests and procedures. The minimum washout period between successive treatments was 1 week.

Assessments

Psychomotor assessments

Critical tracking task The critical tracking task (CTT) (Jex et al. 1966) measures the subject's ability to control a displayed error signal in a compensatory tracking task. Error appears as horizontal deviation of a cursor from midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The frequency of cursor deviations, and therefore its velocity, increases as a stochastic, linear function of time. The subject is required to make compensatory movements with a progressively higher frequency. Eventually, his response frequency lags the error signal in a way that control is lost. The frequency at which control loss occurs is commonly called "lambda-c" (λ_c) or the "critical frequency". The subject performs this test in five trials on each occasion and the mean λ_c is recorded as the final score.

Object movement estimation under divided attention The object movement estimation under divided attention task (OMEDA) (Read et al. 2000) assesses the subject's ability to estimate of speed of movement, and time to contact (TTC) of a moving object to a fixed point under divided attention. The subject is seated in front of a computer screen of which the corners are covered by green triangles and a yellow circle occludes the center of the screen. The occlusion circle varies in size per trial (2, 100, or 200 pixels). From one of the corners, a red dot (target) travels towards the center of the screen. Once it encounters the edge of the occlusion circle, it travels underneath and is no longer visible. The subject has to indicate at what point in time the target reaches the center of the computer screen, by pressing a foot pedal; this is the primary task. During movement of the target, five geometrical shapes appear;

one on top of the occlusion circle and one on top of each of the triangles in the corners. For the secondary task the subject is required to press a button in case the geometric shape at the occlusion circle matches one of the others. Absolute TTC error—defined as the absolute mean difference between estimated and actual TTC—and the number of correct responses to the geometric targets are the primary and secondary measures. The test was originally designed as an off-road driving capacity assessment task.

Actual driving tests

Road tracking test In the road tracking test (O'Hanlon 1984), the subject operates a specially instrumented vehicle over a 100-km primary highway circuit while maintaining a constant speed (95 km/h) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. An electrooptical device mounted at the rear back of the car continuously measures lateral distance separating the vehicle and the left lane-line. This signal is stored on an onboard computer disk for later off line editing wherein all data segments that reveal signal loss, disturbance, or occurrence of passing maneuvers are removed. The remaining data are then used to calculate means and variances for lateral position and speed (SP). Standard deviation of lateral position (SDLP), a measure of road tracking error, is taken as the primary outcome variable. Duration of the test is 1 h.

Car-following test The car-following test (Brookhuis et al. 1994; Ramaekers et al. 2000) involves the use of two vehicles traveling in tandem at speeds of around 70 km/h on a secondary highway. The preceding vehicle is under the control of an investigator. The following vehicle is under the control of the subject who is accompanied by a licensed driving instructor, like in the former test. Subjects attempt to drive 15–30 m behind the preceding vehicle and to maintain that headway as it executes a series of approximately six deceleration maneuvers (sinusoidal speed changes). Between deceleration maneuvers, the investigator in the leading car randomly activates the brake lights of his vehicle while the speed of the leading car remains constant at 70 km/h. The subject is instructed to react to brake lights by removing his/her foot from the speed pedal as fast as possible. This procedure is repeated between 20 and 30 times throughout the test. Dependent variables are brake reaction time (BRT, in milliseconds), and three parameters derived from the analysis of coherence between the speeds of the leading and following car, i.e., time to speed adaptation (TSA, milliseconds), coherence, and gain. Time to speed adaptation, also known as "phase shift", is an estimation for how long it takes the subject to react to speed adaptations of the leading car. The coherence parameter reflects the accuracy of the speed adaptation of the subject. This squared correlation can range from 0, when there is no coherence, to 1, which means that there is perfect coherence. Gain or modulus is an amplification factor between the signals of the two cars. This will be larger than 1 when the subject overreacts to speed adaptations of the leading car. Duration of the test is 25 min.

Subjective measures

Two 10-cm visual analogue driving quality scales, were rated by the subjects at the start (2.5 h postdrug) and the end (4.5 h postdrug) of driving tests, to assess their prediction and evaluation of their driving quality. In addition, the subjects filled out a mental effort scale (Zijlstra 1993) and the addiction research center inventory (ARCI) scale after completing the driving tests. The mental effort scale, a visual analogue scale of 15 cm, assessed the extent to which the subjects experienced the driving tests as mentally demanding. The ARCI contained 49 true–false items, all sensitive to the subjective effects of several classes of abused drugs. Items were clustered into five scales: morphine–benzedrine group (MBG), amphetamine (A), benzedrine group (BG), pentobarbital–chlorpromazine (PCAG), and lysergic acid (LSD) and they measured, respectively, drug-induced euphoria, stimulant-like effects, intellectual efficiency and energy, sedation, and dysphoria (Haertzen 1965; de Wit et al. 2000).

Pharmacokinetic assessments

Blood samples were taken at 1.5 and 5.5 h postdrug, centrifuged immediately, and subsequently frozen at −20°C until analysis for pharmacokinetic assessment. MDMA and MDA concentrations were determined using solid phase extraction and gas chromatography with mass spectrometric detection with quantification limits of 1 ng/ml.

Blood alcohol concentrations were assessed every 15 min during the first 2 h after drinking and at the start and end of driving tests, with a Lion SD-4 Breath Alcohol Analyzer.

Statistical analyses

All statistical analyses were conducted by means of SPSS 11.5 for Windows. Each variable was analyzed using GLM univariate repeated measures procedures with alcohol (two levels) and MDMA (three levels) as main within subject factors. Separate drug-placebo contrasts were conducted after an overall effect of MDMA or the interaction between MDMA and alcohol. The alpha criterion level of significance was set at p=0.05.

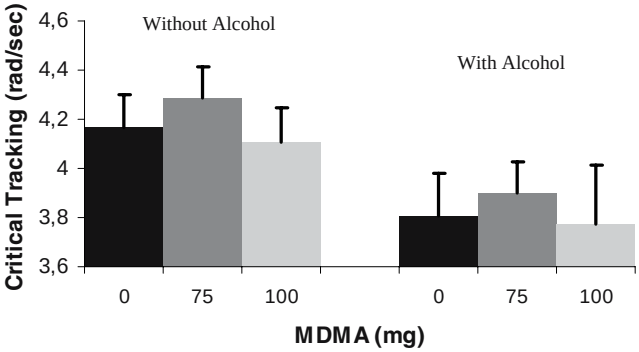

Fig. 1 Mean (SE) critical tracking (rad/seconds) in the CTT during every treatment condition

Results

Missing values

Due to technical dysfunctions, no data were collected in the CTT and the OMEDA on a single occasion. These missing values were replaced in the statistical analysis by the means of the other 17 subjects in that particular treatment condition. There were no missing data in both driving tests.

Failures to complete the driving tests

Four driving tests were terminated before scheduled completion because the driving instructor felt the subjects were unable to continue. These failures to complete the driving tests occurred in different subjects, during treatment with alcohol alone (two times), MDMA 75 and alcohol combined (one time), and placebo (one time). All data from all driving tests entered the statistical analysis.

Psychomotor assessments

Critical tracking task Analysis revealed a significant main effect of alcohol ($F_{1,17}$=17.53; p=0.001) on critical tracking (λ_c) (Fig. 1). Alcohol impaired tracking performance as shown by a decrease in λ_c in alcohol conditions [mean (SE)] [3.82(0.15)] compared to the nonalcohol conditions [4.19(0.12)]. There were no significant effects of MDMA or MDMA by alcohol (Table 1).

Object movement estimation under divided attention There were no significant main effects of alcohol, MDMA, or MDMA by alcohol on the TTC error (Table 1).

Actual driving tests

Road tracking test Analysis revealed significant main effects on SDLP of alcohol ($F_{1,17}$=33.37; p<0.001), MDMA ($F_{2,34}$=12.12; p<0.001), and MDMA by alcohol ($F_{2,34}$= 3.27; p=0.05) (Fig. 2). SDLP increased by 2.5 cm under the influence of alcohol, and decreased by approximately 2 cm after both doses of MDMA, compared with placebo. Inspection of the MDMA–alcohol interaction data showed that the stimulating effect of MDMA 100 mg on SDLP was more prominent when combined with alcohol, whereas the stimulating effect of MDMA 75 mg did not change in magnitude after alcohol coadministration.

Analysis also showed a significant main effect of MDMA ($F_{2,34}$=5.38; p=0.009) on SD speed. Contrast

Table 1 Mean (SE) values of laboratory measures of psychomotor performance and parameters of the actual driving tests

Test	Without alcohol			With alcohol			MANOVA		
	PLA	MDMA 75	MDMA 100	PLA	MDMA 75	MDMA 100	MDMA	ALC	MDMA × ALC
Critical tracking task									
λ_c	4.2 (0.1)	4.3 (0.1)	4.1 (0.1)	3.8 (0.2)	3.9 (0.1)	3.8 (0.1)	–	0.001	–
Object movement estimation under divided attention									
TCC Error	0.4 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	–	–	–
Road tracking task									
SDLP	20.6 (0.9)	18.4 (0.6)	19.0 (0.7)	23.5 (0.9)	22.2 (0.9)	20.2 (0.7)	<0.001	<0.001	0.05
LP	−7.8 (3.4)	−5.1 (5.2)	−6.1 (3.6)	−3.5 (3.9)	−8.0 (3.8)	3.6 (7.5)	–	–	–
Speed	96.6 (0.2)	96.2 (0.3)	96.3 (0.2)	96.4 (0.3)	96.7 (0.2)	96.4 (0.4)	–	–	–
SD(Speed)	2.0 (0.1)	1.8 (0.1)	1.8 (0.2)	2.1 (0.1)	1.8 (0.1)	1.7 (0.1)	<0.05	–	–
Car-following task									
Gain	1.1 (0.0)	1.1 (0.0)	1.1 (0.0)	1.1 (0.0)	1.1 (0.0)	1.1 (0.0)	–	–	–
TSA	1.9 (0.2)	2.2 (0.2)	2.2 (0.2)	2.5 (0.3)	2.0 (0.1)	2.4 (0.1)	–	–	–
BRT	565.0 (30.6)	547.0 (20.1)	548.5 (29.3)	584.6 (28.3)	581.5 (24.8)	624.8 (39.6)	–	0.05	–
Coherence	0.972 (0.004)	0.971 (0.003)	0.971 (0.003)	0.967 (0.005)	0.964 (0.004)	0.967 (0.004)	–	0.014	–

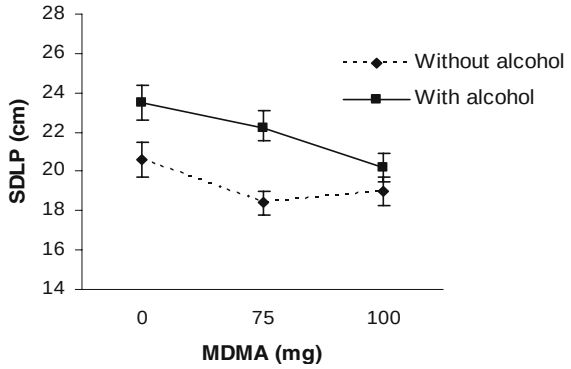

Fig. 2 Mean (SE) standard deviation of lateral position (SDLP, centimeters) in the road tracking test during every treatment condition

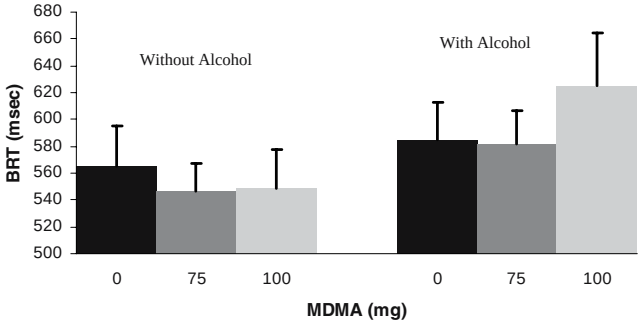

Fig. 3 Mean (SE) brake reaction time (BRT, milliseconds) in the car-following-test during every treatment condition

analysis revealed this effect was due to both the MDMA 75 condition ($F_{1,17}$=8.20; p=0.011) and MDMA 100 condition ($F_{1,17}$=7.44; p=0.014) compared with placebo. Both doses of MDMA significantly decreased SDSP by about 0.2 km/h relative to placebo. There were no effects of alcohol, MDMA, or MDMA by alcohol on lateral position (LP) or speed (Table 1).

Car-following test Analysis revealed significant main effects of alcohol on BRT ($F_{1,17}$=5.76; p=0.028) and coherence ($F_{1,17}$=7.44; p=0.014) (Fig. 3). On the average, alcohol increased brake reaction time by 40 ms. Additional drug–placebo comparisons revealed that both MDMA by alcohol conditions did not differ significantly from placebo.

There were no significant main effects of alcohol, MDMA, or MDMA by alcohol on gain or TSA (Table 1).

Subjective assessments

Before the driving test, subjects predicted a reduction in their driving ability during treatment with alcohol ($F_{1,17}$=16.55; p=0.001) and MDMA ($F_{1.47,24.92}$=19.86; p<0.001). At completion of the driving test, only MDMA was rated to positively affect their driving ability ($F_{2,34}$=11.19; p<0.001). There was no significant interaction effect of MDMA by alcohol. Mental effort during driving significantly increased during alcohol treatment ($F_{1,17}$=6.28; p=0.023) but decreased after MDMA ($F_{1.49;25.35}$=6.18; p=0.011). Further analysis of the MDMA effect showed this effect was caused by the MDMA100 condition (p=0.04); MDMA 75 failed to reach significance (p=0.058). Mental effort was not affected by the MDMA–alcohol combination. ANOVA also revealed significant main effects of MDMA on two scales of the ARCI: i.e., MBG ($F_{2,34}$=14.78 ;p=0.000) and A ($F_{2,34}$=6.31; p=0.005). Subjects felt more euphoric and experienced stimulant-like effects when they received MDMA (both doses), compared with placebo. Furthermore, there were also two significant interaction effects of MDMA by alcohol on PCAG ($F_{2,34}$=4.92; p=0.013) and BG ($F_{2,34}$=5.32; p=0.010). These interactions indicated that alcohol produced sedation and lethargy when given alone, and that combined use with

Table 2 Mean (SE) values of subjective evaluations of driving quality, mental effort, and "drug-induced states"

Test	Without alcohol			With alcohol			MANOVA		
	PLA	MDMA 75	MDMA 100	PLA	MDMA 75	MDMA 100	MDMA	ALC	MDMA × ALC
Predicted driving quality	0.53 (0.25)	2.49 (0.60)	2.58 (.56)	1.33 (0.45)	4.66 (0.49)	4.08 (0.67)	<0.001	0.001	–
Evaluated Driving quality	3.63 (0.65)	2.35 (0.50)	2.26 (0.38)	5.12 (0.65)	3.60 (0.56)	2.08 (0.26)	<0.001	–	–
Mental Effort	4.58 (0.89)	3.92 (0.54)	3.10 (0.48)	6.89 (0.78)	4.19 (0.66)	3.71 (0.53)	0.011	0.023	–
ARCI									
MBG	1.83 (0.29)	3.50 (0.71)	4.11 (0.85)	1.67 (0.59)	4.94 (1.07)	5.22 (0.96)	<0.001	–	–
A	1.11 (0.21)	2.00 (0.48)	2.28 (0.51)	1.06 (0.21)	2.94 (0.68)	2.67 (0.54)	0.005	–	–
BG	1.22 (0.31)	1.22 (0.56)	1.5 (0.60)	−0.22 (0.45)	1.72 (0.55)	1.28 (0.45)	–	–	0.010
PCAG	−0.11 (0.57)	0.28 (0.82)	−0.06 (0.75)	3.17 (0.93)	−0.06 (0.70)	0.11 (0.78)	–	–	0.013
LSD	−1.50 (0.18)	−1.06 (0.30)	−0.72 (0.31)	−1.17 (0.33)	−0.94 (0.27)	−0.89 (0.30)	–	–	–

ARCI scales: *MBG* morphine–benzedrine group (drug-induced euphoria), *A* amphetamine (stimulant-like effects), *BG* benzedrine group (intellectual efficiency and energy), *PCAG* pentobarbital–chlorpromazine (sedation), and *LSD* lysergic acid (dysphoria)

Table 3 Mean (SD) blood alcohol concentrations as a function of time postdosing in alcohol-related treatment conditions (*N*=18)

Time postdrinking (hours)	Time postdrug (hours)	Activity	Alc	MDMA 75/Alc	MDMA 100/Alc
0.5	1.5	Onset laboratory tests	0.65 (0.19)	0.56 (0.12)	0.57 (0.13)
1.25	2.25	End laboratory tests	0.56 (0.16)	0.56 (0.08)	0.58 (0.10)
2 or 3.5	3	Onset CF test	0.38 (0.02)	0.43 (0.03)	0.41 (0.02)
2.5	3.5	Onset road tracking test	0.37 (0.02)	0.41 (0.02)	0.42 (0.02)
4	5	End driving tests	0.29 (0.10)	0.36 (0.07)	0.34 (0.11)

MDMA counteracted feelings of sedation and lethargy (Table 2).

Pharmacokinetics

Mean blood alcohol concentrations (BAC) did not differ significantly between treatments. Mean BACs during performance in the road-tracking test were 0.37, 0.41, and 0.42 mg/ml, respectively, after placebo, MDMA 75 mg, and MDMA 100 mg. During car-following, mean BACs varied from 0.38, 0.43 and 0.41 mg/ml, respectively, after placebo, MDMA 75 mg, and MDMA 100 mg. Descriptive parameters of BAC, MDMA, and its main metabolite MDA are given in Tables 3 and 4.

Discussion

Actual driving performance was affected by alcohol, MDMA, and the combination of both substances. MDMA caused a reduction in SDLP (weaving) and SDSP in the road-tracking test. Under the influence of both MDMA doses (75 and 100 mg) SDLP decreased by 2 cm. This is in line with results of a previous study, in which a similar reduction in SDLP after single doses of MDMA was also shown (Ramaekers et al. 2006, in press). Alcohol, in contrast, detrimentally affected driving performance by producing an increase in weaving by 2.5 cm compared to placebo. Alcohol-related increments in SDLP dropped to 1.5 cm in combination with MDMA 75 mg and even reduced to zero in combination with MDMA 100 mg. These data seem to indicate that the stimulatory effect of MDMA on road tracking performance was present both in the absence and in the presence of alcohol, and perhaps even stronger so in the presence of alcohol as suggested by the significant MDMA–alcohol interaction. Car-following performance, however, remained unaffected by MDMA while alcohol alone increased brake reaction time. Brake reaction time increased by 20 ms when alcohol was given alone or in combination with 75 mg of MDMA, compared with placebo. When combined with 100 mg MDMA, brake reaction time even increased by 60 ms compared with placebo. These data thus seem to suggest that MDMA may worsen the impairing effects of alcohol on reaction time performance. However, the MDMA by alcohol interaction term failed to reach significance at the statistical level. In any case, it is clear that MDMA did not reduce the impairing effects of alcohol in the car-following task. This is in line with previous results showing that the stimulant effects of MDMA were not sufficient to overcome alcohol-induced impairment of impulse control or risk-taking behavior (Ramaekers and Kuypers 2006).

Psychomotor performance (critical tracking, OMEDA) was not affected by MDMA. It is noteworthy that both critical tracking and OMEDA task performance were shown to change after acute MDMA administration in a previous study by our group (Lamers et al. 2003). That study showed that a single dose of MDMA 75 mg improved tracking performance and decreased the subjects' ability to estimate time to contact in the OMEDA task. The investigators employed a more demanding and complex version of the OMEDA and they measured tracking performance repeatedly between 2 and 5 h postdosing, i.e., closer to T_{max}, which may have increased the sensitivity of these tests for MDMA effects. This explanation, however, remains highly speculative because

Table 4 Mean (SD) concentrations (ng/ml) of MDMA and MDA at 1.5 and 5.5 h postdosing in every treatment condition (*N*=18)

Time postdrug (hours)	Activity		MDMA 75	MDMA 100	MDMA 75/Alc	MDMA 100/Alc
1.5	Onset laboratory tests	MDMA	137.4 (31.9)	191.8 (49.1)	147.1 (36.3)	208.5 (45.7)
		MDA	3.5 (1.2)	4.5 (1.5)	3.4 (1.0)	4.7 (1.4)
5.5	End driving tests	MDMA	113.5 (31.2)	163.0 (40.7)	107.9 (25.4)	152.6 (40.8)
		MDA	6.8 (1.7)	9.0 (1.9)	6.5 (1.5)	8.8 (2.1)

MDMA/MDA plasma concentrations in the present study were comparable at the onset and completion of each test session, which suggests that drug levels were stable throughout testing. Alcohol, on the other hand, significantly impaired critical tracking performance as expected. Combined administration of MDMA and alcohol produced impairments in the critical tracking task that were comparable to alcohol alone. Alcohol-induced impairment was thus not mitigated by coadministration of MDMA.

Pharmacokinetics of MDMA were expected to be nonlinear based on a study of de la Torre et al. (2004) who showed that blood plasma concentrations rose nonproportionaly when giving MDMA in doses ranging from 50 to 150 mg to a restricted number of subjects. Based on this information, doses in the current study were selected in proximity. Resulting blood plasma concentrations did not reveal an exponential relation. Nevertheless, the values did not differ much from those found by de la Torre et al. (2004). They showed actually a more or less linear relation between the 75- and 100-mg dose but nonlinear relations when taking into account the extreme doses of 50 and 150 mg. It was also expected that plasma concentrations of MDMA would increase when combined with alcohol (de la Torre et al. 2000). Hernandez-Lopez et al. (2002) showed an increase of 13% when combining a 100-mg dose of MDMA with 0.8 g/kg ethanol. Our data showed increases of 7 and 8.7%, respectively, when 75 and 100 mg MDMA was combined with alcohol. There was no significant difference between the mean MDMA concentrations in the alcohol condition vs the MDMA only condition for both dose regimes. Mean MDMA concentrations at 1.5 and 5.5 h after administration of 75 and 100 mg dose, and intersubject variabilities were in agreement with data published in other studies (Mas et al. 1999; de la Torre et al.2000).

When under the influence of alcohol, subjects experienced they had to invest more effort when performing on the driving tasks. Their subjective experience supported objective measures of alcohol impairments of actual driving. However, their impression that they drove better after intake of MDMA and had to invest less effort was only partly reflected in objective measures: i.e., a reduction in SDLP. The results from ARCI were in line with those of a study by Hernandez-Lopez et al. (2002). MDMA alone produced euphoria and stimulant-like effects, and when given in combination with alcohol, MDMA counteracted the effects of the alcohol-induced sedation and lack of energy. In addition, and similar to the results of Hernandez-Lopez et al. (2002), MDMA counteracted the subjective impairment of alcohol but not the objective psychomotor impairment of alcohol.

Collectively, these data indicate that MDMA is a stimulant drug that may facilitate a certain aspect of driving, i.e., road tracking. However, performance compensation after combined MDMA–alcohol administration was limited to a single driving parameter and was never sufficient to fully overcome alcohol impairment in all driver tasks.

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