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Effects of a beta-blocker on the cardiovascular response to MDMA (Ecstasy)

Cédric M. Hysek, Franz X. Vollenweider, Matthias E. Liechti

Institutions: University Hospital of Basel, University of Zurich

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Hysek, C M ; Vollenweider, F X ; Liechti, M E

Abstract: BACKGROUND: MDMA (3,4-methylenedioxymethamphetamine, 'Ecstasy') produces tachycardia and hypertension and is rarely associated with cardiovascular and cerebrovascular complications. In clinical practice, beta-blockers are often withheld in patients with stimulant intoxication because they may increase hypertension and coronary artery vasospasm due to loss of beta(2)-mediated vasodilation and unopposed alpha-receptor activation. However, it is unknown whether beta-blockers affect the cardiovascular response to MDMA. METHODS: The effects of the non-selective beta-blocker pindolol (20 mg) on the cardiovascular effects of MDMA (1.6 mg/kg) were investigated in a double-blind placebo-controlled crossover study in 16 healthy subjects. RESULTS: Pindolol prevented MDMA-induced increases in heart rate. Peak values (mean+/-SD) for heart rate were 84+/-13 beats/min after MDMA vs 69+/-7 beats/min after pindolol-MDMA. In contrast, pindolol pretreatment had no effect on increases in mean arterial blood pressure (MAP) after MDMA. Peak MAP values were 115+/-11 mm Hg after MDMA vs 114+/-11 mm Hg after pindolol-MDMA. Pindolol did not change adverse effects of MDMA. CONCLUSION: The results of this study indicate that beta-blockers may prevent increases in heart rate but not hypertensive and adverse effects of MDMA.

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C M Hysek,[1] F X Vollenweider,[2] M E Liechti[1]

[1]Division of Clinical Pharmacology and Toxicology and Department of Biomedicine, University Hospital and University of Basel, Switzerland
[2]Heffter Research Center, University Hospital of Psychiatry, Zurich, Switzerland

Correspondence to
Matthias Liechti, Division of Clinical Pharmacology and Toxicology, Department of Internal Medicine, University Hospital Basel, Hebelstasse 2, CH-4031 Basel, Switzerland; mliechti@uhbs.ch

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ABSTRACT

Background MDMA (3,4-methylenedioxymethamphetamine, 'Ecstasy') produces tachycardia and hypertension and is rarely associated with cardiovascular and cerebrovascular complications. In clinical practice, β-blockers are often withheld in patients with stimulant intoxication because they may increase hypertension and coronary artery vasospasm due to loss of β_2-mediated vasodilation and unopposed α-receptor activation. However, it is unknown whether β-blockers affect the cardiovascular response to MDMA.

Methods The effects of the non-selective β-blocker pindolol (20 mg) on the cardiovascular effects of MDMA (1.6 mg/kg) were investigated in a double-blind placebo-controlled crossover study in 16 healthy subjects.

Results Pindolol prevented MDMA-induced increases in heart rate. Peak values (mean±SD) for heart rate were 84±13 beats/min after MDMA vs 69±7 beats/min after pindolol-MDMA. In contrast, pindolol pretreatment had no effect on increases in mean arterial blood pressure (MAP) after MDMA. Peak MAP values were 115±11 mm Hg after MDMA vs 114±11 mm Hg after pindolol-MDMA. Pindolol did not change adverse effects of MDMA.

Conclusion The results of this study indicate that β-blockers may prevent increases in heart rate but not hypertensive and adverse effects of MDMA.

INTRODUCTION

MDMA (3,4-Methylenedioxymethamphetamine) is the main compound contained in 'Ecstasy' pills. Acute adverse effects of MDMA include hyperthermia leading to rhabdomyolysis and multiorgan failure, hyponatraemic cerebral oedema, acute liver failure, serotonin syndrome and acute panic reactions.[1 2] Rarely, MDMA has been associated with vascular events such as myocardial infarction, subarachnoid and intracranial haemorrhage and cerebral infarction.[3 4] These vascular complications may arise from cardiostimulant and hypertensive effects of MDMA.[5] β-Adrenergic antagonists are commonly used in the treatment of myocardial ischaemia and hypertension. However, in the case of intoxications with cocaine or other stimulants, the use of β-blockers is controversial because β-blockade is thought to worsen hypertension and coronary artery vasospasm through unopposed α-receptor activation.[6–8] It is unknown whether—and, if so, how—β-blockers affect cardiovascular responses to MDMA. We assessed the effects of the non-selective β-blocker pindolol on the haemodynamic effects of MDMA in healthy subjects.

METHODS

Participants

The use of MDMA in healthy subjects was authorised by the Swiss Federal Health Office. Sixteen male volunteers (age 25±4 years, range 20–36) were included in the study. Subjects were recruited from University Hospital staff or were students at the Medical School of the University of Zurich. All volunteers provided written consent after being informed about the aims and design of the study and potential risks associated with MDMA and pindolol use. Subjects were screened to be physically and mentally healthy according to medical history, physical examination, ECG and blood analyses, and were screened by a structured psychiatric interview based on a computerised diagnostic expert system.[9] Exclusion criteria were personal or family histories of mental diagnostic and statistical manual of mental disorders (DSM IV) axis I disorders, hypertension, cardiovascular or neurological disorders, use of medications and prior illicit drug use (except tetrahydrocannabinol-containing products) on more than five occasions. All subjects engaged in regular physical exercise. Apart from sporadic use of cannabis, one subject reported a single previous experience with a hallucinogenic drug (psilocybin), two subjects had previously used both MDMA and a hallucinogen, and seven subjects were drug-naïve. Subjective (primary outcome) and neurocognitive results from the present study have previously been reported.[10] Here we present the previously unpublished cardiovascular and adverse effects (secondary outcomes) of the same study subjects[10] with one additional subject.

Study design and setting

A double-blind placebo-controlled single-dose crossover design was used with four treatment conditions (placebo–placebo, pindolol–placebo, placebo–MDMA or pindolol–MDMA) and a 2-week washout time between sessions. This design has the main advantage that subjects act as their own control. Treatment order was pseudo-random and counterbalanced to avoid time order effects. The duration of the trial for an individual subject was 6–10 weeks. Placebo or pindolol was given to the subjects at 09.00 h on each of the four study days. Sixty minutes later MDMA or placebo was administered. Blood pressure, heart rate and body temperature were measured at 0, 30, 60, 90, 120, 150, 180, and 210 min after pindolol–placebo administration (−60, −30, 0, 30, 60, 90, 120 and 150 min after MDMA–placebo administration). Blood pressure and heart rate were registered by an ERKA ambulatory blood pressure measuring system

(ERKA.OS 90-2, Kallmeyer Medizintechnik GmbH, Bad Tölz, Germany) in the non-dominant arm after a resting time of 5 min with the volunteer sitting in an arm chair with the back supported. Measures were taken once per time point. Between measurements, subjects were allowed to engage in non-strenuous activities such as reading, listening to music or walking around in the testing room. Most of the time subjects were sitting in an armchair or lying on a couch. Body temperature was measured with an axillary thermometer (Terumo C202 Terumo Corp, Tokyo, Japan). Acute adverse effects were assessed 135 min after pindolol–placebo (75 min after MDMA–placebo) administration by the List of Complaints.[5 11] This scale consists of 66 items yielding a total adverse effects score (non-weighted sum of the item answers) reliably measuring physical and general discomfort. The scale has previously been shown to be sensitive to the effects of pharmacological pretreatments on the adverse effects of MDMA.[12 13] Subjective and cognitive drug effects were measured as reported elsewhere.[10]

Substances

(±)-MDMA hydrochloride (Lipomed, Arlesheim) was obtained from the Swiss Federal Health Office. Subjects received MDMA at a dose of 1.6 mg/kg (mean±SD dose 122±14 mg). This dose of MDMA corresponds to a typical recreational dose of Ecstasy and produces robust psychological and physiological effects.[5] Pindolol (Visken, Novartis Pharma, Basel, Switzerland) was used in a dose of 20 mg. Pindolol is a non-selective β-blocker with intrinsic activity and additional serotonergic $5HT_1$-receptor-blocking properties. We selected pindolol for this study and a dose of 20 mg because this dose produces approximately 40% brain $5\text{-}HT_{1A}$ receptor occupancy,[14] and we were also interested in the role of $5\text{-}HT_1$ receptors in the mediation of the subjective effects of MDMA based on behavioural studies in rats.[15–17] Pindolol is commonly used in doses of 5–30 mg per day divided into two daily doses in the treatment of arterial hypertension. Thus, a single dose of 20 mg of pindolol corresponds to a moderate to high therapeutic dose. Pindolol pretreatment slightly attenuated positive derealisation associated with MDMA and did not alter MDMA-induced impairment of cognitive performance as described in detail elsewhere.[10]

Data analysis

All analyses were performed with STATISTICA Version 6.0 (StatSoft Inc, Tulsa, USA). We determined the peak effect in the 150 min after MDMA–placebo administration (time points 60–210 min) and the area under the curve (AUC) of the effects versus time curve calculated by the trapezoidal rule for each value (time points 60–210 min). These individual peak effects and AUC values for each outcome variable were analysed by one-way repeated measures analysis of variance (ANOVA) with treatment condition (placebo–placebo, pindolol–placebo, placebo–MDMA and pindolol–MDMA) as within-subject factor. Post hoc comparisons were performed using Tukey tests based on significant main effects of treatment condition in the omnibus ANOVA. The absence of treatment order and carryover effects was confirmed by ANOVA with treatment order (1–4) as within-subject factor. Treatment effects were also analysed over time with two-way repeated measures ANOVA with treatment condition and time as within-subject factors followed by Tukey tests based on significant treatment by time interactions in the omnibus ANOVA. We controlled for deviations from multivariate normality using Mauchley tests of sphericity. Greenhouse and Geisser corrections were used where necessary to adjust for deviations from multivariate normality. These analyses yielded similar results to those using peak and AUC values. The criterion for significance was set at $p<0.05$. Mean arterial blood pressure (MAP) was calculated from diastolic blood pressure (DBP) and systolic blood pressure (SBP) using the following formula: MAP=DBP+(SBP−DBP)/3. A decrease in MAP of 5 mm Hg was considered clinically relevant and similar to the previously reported one for the effects of citalopram on MDMA-induced increases in blood pressure.[12] A sample size of 15 achieves 97% power to detect a difference of 5 between the null hypothesis mean of −5 and the alternative hypothesis mean of 0 with a known SD of the difference of 5[12] and with a significance level (α) of 0.05 using a two-sided one-sample t test.

RESULTS

Cardiovascular effects and body temperature

The results are shown in figure 1. All 16 subjects completed all four study sessions. ANOVA showed that the four treatment conditions overall resulted in significantly different peak levels of heart rate and MAP across sessions (main effects: $F(3,45)=28.7$, $p<0.001$; $F(3,45)=47.9$, $p<0.001$; respectively). MDMA significantly increased peak values for heart rate by (mean±SD) 15±10 beats/min ($p<0.01$) compared with placebo. Pindolol prevented the MDMA-induced increase in heart rate ($p<0.001$ for placebo–MDMA vs pindolol–MDMA) but had no effect on heart rate when given alone compared with placebo. MDMA significantly increased peak MAP by 16±8 compared with placebo ($p<0.001$). Pindolol had no effect on the peak MAP response to MDMA. The MDMA-induced increase in peak body temperature (0.2±0.3°C compared with placebo) was not significant. Pindolol had no effect on MDMA-induced elevations in body temperature.

Adverse effects

MDMA significantly increased acute adverse effects scores (main effect of treatment: $F(3,45)=10.3$, $p<0.001$, post hoc test: $p<0.001$ for MDMA vs placebo). The most frequently reported acute side effects of MDMA were impaired balance, lack of appetite, thirst, feelings of restlessness or restless legs, difficulty concentrating and feeling cold or warm. None of the subjects reported chest pain. Pindolol did not change the adverse effects of MDMA.

DISCUSSION

The β-blocker pindolol prevented MDMA-induced tachycardia but not hypertension or other adverse effects associated with MDMA. Pindolol is an antagonist at central serotonin $5\text{-}HT_1$ receptors.[14] As described in detail elsewhere,[10] pindolol moderately attenuated MDMA-induced increases in positive mood, dreaminess, derealisation and mania-like experience, indicating a possible role for serotonergic $5\text{-}HT_1$ receptors in the mediation of these mood effects of MDMA. In contrast, pindolol had no effect on MDMA-induced cognitive performance impairment.[10] In addition, the effect of pindolol pretreatment on the subjective response to MDMA was weak compared with that of the serotonin uptake transporter blocker citalopram,[12 18] which is thought to block the interaction of MDMA with the serotonin transporter so inhibits the release of serotonin from presynaptic nerve terminals.

We are not aware of reports on the effects of β-blockers on the haemodynamic effects of amphetamines including MDMA. The β-blocker propranolol decreases heart rate[19 20] and decreases[20] or increases[19] blood pressure in patients with acute cocaine intoxication. In a placebo-controlled study, the α-β-blocker carvedilol increased both heart rate and blood pressure in response to

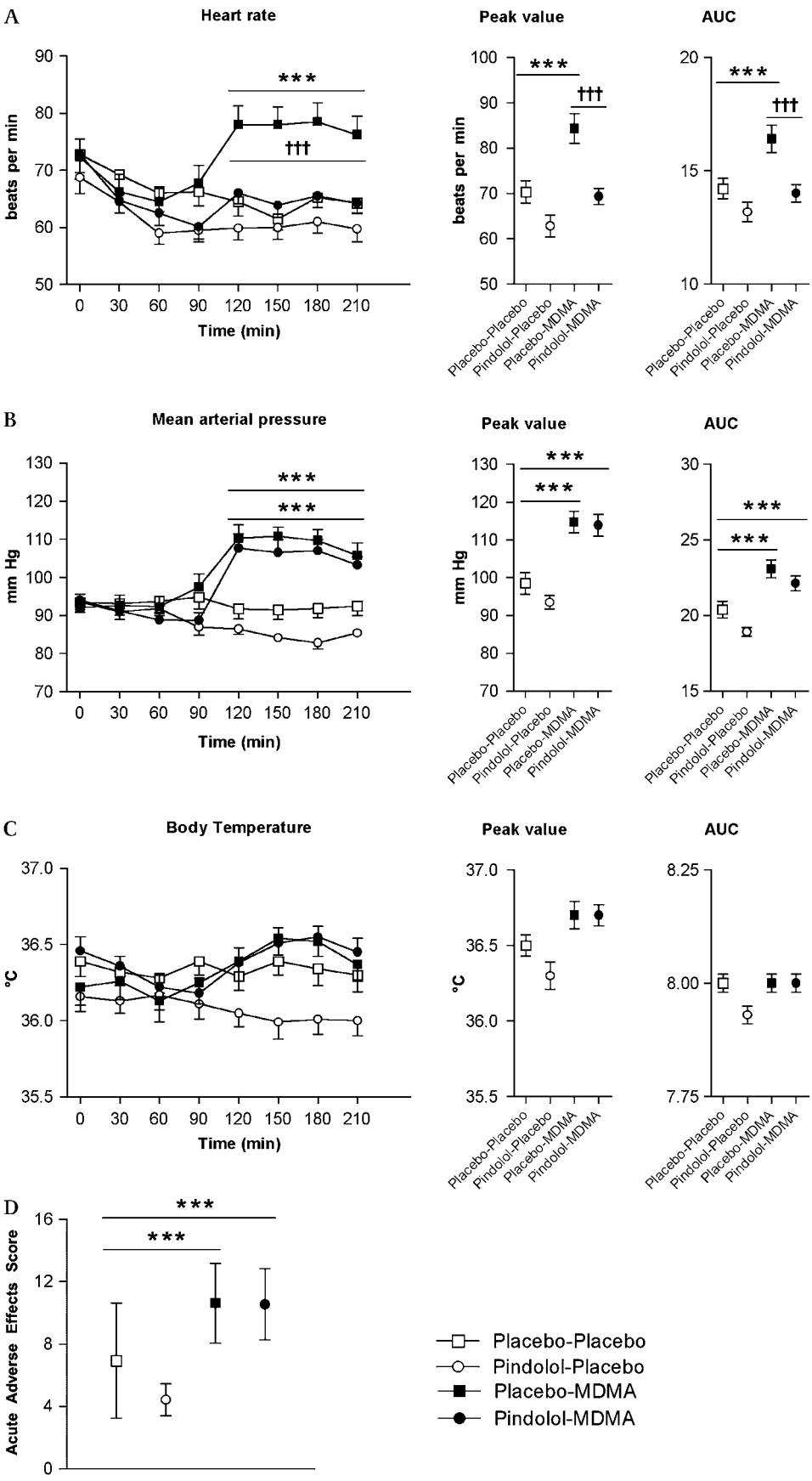

Figure 1 Graphs from left to right show drug effects over time, peak values (60—210 min) and area under the curve values (AUC from 60 to 210 min$\times 10^{-3}$). (A) Pindolol pretreatment prevented the MDMA-induced increase in heart rate. (B) Pindolol had no effect on MDMA-induced increases in mean arterial blood pressure. (C) Pindolol had no effect on the non-significant increase in body temperature associated with MDMA. (D) Pindolol did not change adverse effects associated with MDMA. *$p<0.05$ and ***$p<0.001$ placebo-MDMA vs placebo-placebo, †$p<0.05$ and †††$p<0.001$ placebo-MDMA vs pindolol-MDMA. Values represent mean±SE of 16 subjects.

smoked cocaine when carvedilol was used at a low dose which preferentially blocks β-receptors.[21] At a higher dose, which blocks both α- and β-receptors, carvedilol decreased all haemodynamic effects of cocaine.[21] The α-β-blocker labetolol, which has a higher relative affinity for the α-receptor than carvedilol, dose-dependently prevented all haemodynamic effects of smoked or

intranasal cocaine.[6 22] Furthermore, propranolol, but not labetalol, potentiated cocaine-induced coronary vasoconstriction.[6 7] Together these studies indicate that β-blockade without α-blockade has no effect or may even increase cocaine-induced hypertension, possibly due to unopposed α-receptor stimulation and increased vasoconstriction. Our results extend these findings and suggest that β-blockade affects MDMA-induced tachycardia but does not influence the blood pressure and adverse effects of MDMA. Severe MDMA toxicity such as multiorgan failure results from hyperthermia and not solely from tachycardia.[1] Heart rate is an easily determined marker of the severity of MDMA poisoning and β-blockade may mask this MDMA effect, during which time serious MDMA toxicity develops.

The present study has several limitations. Pindolol is a non-selective β-receptor blocker with intrinsic activity, unlike the β_1-selective β-blockers that are mostly used today and that may interact differently with MDMA. Pindolol was used because this compound also blocks serotonergic 5-HT_1 receptors and the primary aim of this study was to investigate the role of 5-HT_1 in the subjective effects of MDMA in humans. This focus was also the reason why pindolol was given before MDMA. Treatment after MDMA would have more closely mirrored the clinical situation where treatment for cardiovascular stimulation associated with intoxication with Ecstasy would be initiated following ingestion of MDMA. Treatment with a β-blocker after MDMA administration may result in less effective blockade of the effects of MDMA due to the delayed availability of the blocker at the site of action, but is unlikely to result in a qualitatively different pharmacodynamic interaction. Only single doses of pindolol and MDMA were used in the present study. However, the significant interactive effects of pindolol and MDMA on heart rate indicate that effective doses of both compounds were used. Nevertheless, different doses could interact differently. We do not know how the haemodynamic changes observed in our study would translate into actual risk changes for vascular complications. For example, the beneficial effects of β-blockers on heart rate and cardiac oxygen consumption may outweigh the potential harm of theoretically unopposed α-stimulation.[23] Finally, the present study was performed using pure MDMA in healthy subjects who were not engaged in physical activities and were seated in a quiet research environment. In contrast, recreational users of MDMA may be dancing and are likely to ingest other substances in addition to MDMA including cocaine or other amphetamines and may also show significant co-morbidity.[2] The findings from this study can therefore not be generalised to the treatment of patients with cardiovascular complications associated with recreational MDMA use. Nevertheless, our results indicate that β-blockers would not be expected to worsen the cardiovascular and adverse effects of MDMA. In addition, subjects on β-blocker medication are likely to show similar blood pressure responses to MDMA as those without medication.

In conclusion, β-blockers may prevent tachycardia but not blood pressure responses or adverse effects associated with MDMA. The role of α-β-blockade in the treatment of MDMA intoxications needs further evaluation. Furthermore, MDMA stimulates the sympathetic nervous system centrally rather than peripherally,[1 24 25] so centrally-acting sedative agents (eg, benzodiazepines) should be used as first-line treatments in cases of MDMA or other stimulant intoxication.[1 26 27]

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Competing interests None.

Ethics approval This study was conducted with the approval of the ethics committee of the University Hospital of Zurich.

Contributors MEL and FXV conceived the study and obtained research funding. FXV supervised the conduct of the trial and data collection. CMH and MEL analysed and interpreted the data. CMH and MEL wrote the paper. MEL takes responsibility for the paper as a whole.

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