



Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone or in combination

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Abstract

Methylphenidate and 3,4-methylenedioxyamphetamine (MDMA, 'ecstasy') are widely misused psychoactive drugs. Methylphenidate increases brain dopamine and norepinephrine levels by blocking the presynaptic reuptake transporters. MDMA releases serotonin, dopamine and norepinephrine through the same transporters. Pharmacodynamic interactions of methylphenidate and MDMA are likely. This study compared the pharmacodynamic and pharmacokinetic effects of methylphenidate and MDMA administered alone or in combination in healthy subjects using a double-blind, placebo-controlled, crossover design. Methylphenidate did not enhance the psychotropic effects of MDMA, although it produced psychostimulant effects on its own. The haemodynamic and adverse effects of co-administration of methylphenidate and MDMA were significantly higher compared with MDMA or methylphenidate alone. Methylphenidate did not change the pharmacokinetics of MDMA and vice versa. Methylphenidate and MDMA shared some subjective amphetamine-type effects; however, 125 mg of MDMA increased positive mood more than 60 mg of methylphenidate, and methylphenidate enhanced activity and concentration more than MDMA. Methylphenidate and MDMA differentially altered facial emotion recognition. Methylphenidate enhanced the recognition of sad and fearful faces, whereas MDMA reduced the recognition of negative emotions. Additionally, the present study found acute pharmacodynamic tolerance to MDMA but not methylphenidate. In conclusion, the combined use of methylphenidate and MDMA does not produce more psychoactive effects compared with either drug alone, but potentially enhances cardiovascular and adverse effects. The findings may be of clinical importance for assessing the risks of combined psychostimulant misuse. Trial registration identification number: NCT01465685 (<http://clinicaltrials.gov/ct2/show/NCT01465685>).

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Introduction

Methylphenidate is used for the treatment of attention-deficit/hyperactivity disorder and misused as a cognitive enhancer and recreationally (McCabe et al., 2005). 3,4-methylenedioxyamphetamine (MDMA; 'ecstasy') is a popular recreational drug. People who frequently use ecstasy often also use methylphenidate (Wilkins et al., 2011). Methylphenidate inhibits the dopamine (DA) and norepinephrine (NE) transporters (DAT and NET) (Han and Gu, 2006), thereby elevating DA and NE levels in the brain (Schmeichel and Berridge, 2013). MDMA releases brain serotonin (5-hydroxytryptamine (5-HT)),

NE and DA through their corresponding reuptake transporters (Verrico et al., 2007; Hysek et al., 2012d). Because both methylphenidate and MDMA act at the DAT and NET, pharmacodynamic drug–drug interactions can be expected, but have not been evaluated. Therefore, the present clinical study assessed the pharmacodynamic and pharmacokinetic interactions between methylphenidate and MDMA in healthy volunteers.

MDMA-induced monoamine release is blocked by monoamine transporter inhibitors (Verrico et al., 2007; Rothman et al., 2010; Hysek et al., 2012d). Inhibition of the 5-HT transporter (SERT) (Liechti et al., 2000; Farre et al., 2007) or NET (Hysek et al., 2011) attenuated the pharmacodynamic response to MDMA in healthy subjects. Whether the DAT contributes to the effects of MDMA in humans has not yet been tested. Methylphenidate inhibits the transport of MDMA into cells and MDMA-induced release of DA and NE (Verrico et al., 2008; Hysek et al., 2012d). We hypothesized that

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methylphenidate may attenuate the emotional, autonomic and endocrine effects of MDMA to the extent that they depend on the DAT/NET-mediated release of DA/NE. We did not anticipate any pharmacokinetic methylphenidate-MDMA interactions because methylphenidate is metabolized by carboxylesterase 1 (Sun et al., 2004), and MDMA is primarily metabolized by cytochrome P450 (CYP) 2D6 (de la Torre et al., 2012). Thus, we expected pharmacodynamic methylphenidate-MDMA interactions in the absence of pharmacokinetic interactions.

Additionally, the present study directly compared the emotional, autonomic, endocrine and pharmacological effects of methylphenidate and MDMA in the same subjects.

Methods

Participants

Sixteen healthy subjects (eight men and eight women; mean age 24.8 ± 2.6 yr) were recruited from the University of Basel campus. Subjects with a personal or first-degree relative history of psychiatric disorders or chronic or acute physical illness were excluded as previously described (Hysek et al., 2012b, c). Additional exclusion criteria were smoking and a lifetime history of using illicit drugs more than five times, with the exception of past cannabis use. Thirteen subjects had used cannabis at some time in their lives. Eleven subjects had minimal previous experience with other illicit drugs (2–4 times). Six subjects had used ecstasy, three had used a stimulant, one had used an hallucinogen and three had used nitrous oxide. The use of any illicit drugs, including cannabis, within the past two months or during the study period was prohibited. We performed urine drug tests at screening and before each test session using TRIAGE 8 (Biosite, USA). Female participants were investigated during the follicular phase of their menstrual cycle (day 2–14) to account for cyclic changes in the reactivity to amphetamines. Because MDMA is metabolized primarily by CYP2D6, all of the subjects, with the exception of one, were phenotyped for CYP2D6 activity using dextromethorphan as the probe drug. The study had 12 extensive, two intermediate, and one poor CYP2D6 metabolizer.

Study design

This was a double-blind, placebo-controlled, cross-over study with four experimental test sessions (placebo–placebo, methylphenidate–placebo, placebo–MDMA, and methylphenidate–MDMA) performed in randomized and counterbalanced order. This means that all of the subjects received all of the study treatments in a powerful within-subjects study design. The washout periods between sessions were at least 10 d. The study was conducted at the University Hospital of Basel in accordance with

the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the Ethics Committee of the Canton of Basel, Switzerland, and the Swiss Agency for Therapeutic Products (Swissmedic). The study was registered at ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/show/NCT01465685>). All of the subjects provided written informed consent and were debriefed and paid at study completion.

Study outline

The study included a prescreening telephone interview, a screening visit, four whole-day test sessions with a next-day follow-up and an end-of-study visit. Study sessions began at 07:45 hours. An indwelling intravenous catheter was placed in an antecubital vein for blood sampling, and baseline measurements were performed. Methylphenidate (60 mg) or placebo was administered at 08:00 hours. MDMA (125 mg) or placebo was administered at 09:00 hours. A standardized lunch was served at 12:00 hours, and the subjects were sent home at 18:00 hours. On the day following each test session, the participants returned to the research ward at 09:00 hours for the assessment of adverse effects and blood sampling. The sessions occurred in a hospital research ward with a maximum of two participants present per session. The subjects sat or laid comfortably and did not engage in physical activities.

Drugs

±MDMA hydrochloride (Lipomed AG, Switzerland) was prepared as gelatin capsules (100 and 25 mg). Identical placebo (mannitol) capsules were prepared. MDMA was administered in a single absolute dose of 125 mg, corresponding to 1.87 ± 0.21 mg/kg body weight (mean \pm s.d.). Immediate-release methylphenidate tablets (10 mg, Ritalin, Novartis AG, Switzerland) were encapsulated within opaque gelatin capsules, and identical placebo (mannitol) capsules were prepared. One hour before MDMA administration, methylphenidate was administered in a single dose of 60 mg, corresponding to 0.90 ± 0.1 mg/kg body weight (mean \pm s.d.). This dosing interval resulted in maximal plasma concentration (C_{\max}) values of methylphenidate shortly before the C_{\max} of MDMA was reached.

Measures

Pharmacodynamics

Autonomic effects. Blood pressure, heart rate and tympanic body temperature were assessed repeatedly before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h after MDMA/placebo administration, as previously described in detail (Hysek and Liechti, 2012). The cardiovascular measures were performed in duplicate after a resting time of 10 min and the averages were used for the analyses.

Psychometric scales. Subjective effects were repeatedly assessed using previously described psychometric scales. The 60-item short version of the Adjective Mood Rating Scale (AMRS; Janke and Debus, 1978) was administered before and 1.25, 2, 5 and 24 h after MDMA/placebo administration. The German version of the 49-item Addiction Research Center Inventory (ARCI; Martin et al., 1971) was administered 1 h before and 2.5 and 5 h after MDMA/placebo administration. Visual Analog Scales (VASs; Hysek et al., 2011, 2012b) were administered 1 h before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 24 h after MDMA/placebo administration. The 5-Dimensions of Altered States of Consciousness Rating Scale (5D-ASC; Studerus et al., 2010) was used 5 h after MDMA/placebo administration to retrospectively rate the effects of the drugs.

Emotion recognition task. We used a previously described Facial Emotion Recognition Task that is sensitive to MDMA (Bedi et al., 2010). The task was performed 1.5 h after MDMA/placebo administration during the peak effects of the drugs. The task included 10 neutral faces and 160 faces that expressed one of four basic emotions (i.e. happiness, sadness, anger or fear), with pictures morphed between 0% (neutral) and 100% in 10% steps. Two female and two male pictures were used for each of the four emotions. Stimuli were shown in a randomized order for 500 ms and were then replaced by the rating screen. The participants had to indicate the correct emotion. The outcome measure was accuracy.

Adverse effects. Adverse effects were assessed before and 5 and 24 h after MDMA or placebo administration using the 66-item List of Complaints (Zerssen, 1976). The scale yields a total adverse effects score, reliably measuring physical and general discomfort.

Endocrine and pharmacokinetic measures

Blood samples to determine concentrations of catecholamines (i.e. NE and epinephrine) were collected at baseline and 1 and 2 h after MDMA/placebo administration. Free catecholamine plasma concentrations were determined using ultraperformance liquid chromatography-mass spectrometry/mass spectrometry (UPLC-MS/MS; Dunand et al., 2013). Plasma cortisol and prolactin levels were measured at baseline and 2 h after MDMA/placebo administration using radioimmunoassays (Hysek et al., 2012a). Blood samples for the determination of MDMA, 3,4-methylenedioxamphetamine (MDA), 4-hydroxy-3-methoxymethamphetamine (HMMA) and methylphenidate were collected 1 h before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 24 h after MDMA/placebo administration. Plasma MDMA, MDA and HMMA concentrations were determined using high-performance LC-MS/MS, as described previously (Hysek et al., 2012c, 2013), and methylphenidate was added as an additional analyte.

The detection limits were 1 ng/ml for MDMA, MDA, HMMA and methylphenidate. Interday precision values (CV) ranged from 3.2 to 8.8%, and interday accuracy values ranged from 86.8 to 106.4% for all of the analytes.

Statistical and pharmacokinetic analyses

Subjective effects, catecholamine levels and body temperature values were transformed to differences from baseline. Peak effect (E_{\max}) values were determined for all repeated measures. E_{\max} values were analysed by repeated-measures analysis of variance (ANOVA), with MDMA (MDMA *vs.* placebo) and methylphenidate (methylphenidate *vs.* placebo) as the within-subjects factors, using STATISTICA 11 (StatSoft, USA). Tukey's *post-hoc* comparisons were performed based on significant main effects or interactions. Additional ANOVAs were performed with drug order to exclude carry-over effects. The criterion for significance was $p < 0.05$. Pharmacokinetic data were analysed using non-compartmental models. C_{\max} and the time to maximal plasma concentration (T_{\max}) were obtained directly from the observed concentration-time curves. The terminal elimination rate constant (λ_z) was estimated by log-linear regression after semilogarithmic transformation of the data using at least three data points of the terminal linear phase of the concentration-time curve. Terminal elimination half-life ($t_{1/2}$) was calculated using λ_z and the equation $t_{1/2} = \ln 2 / \lambda_z$. The area under the plasma time curve (AUC_{0-24h}) was calculated using the linear trapezoidal rule.

Results

Pharmacodynamics

Pharmacodynamic peak effects and statistics are shown in Table 1.

Autonomic effects

MDMA produced significantly higher increases in systolic blood pressure than methylphenidate ($p < 0.01$, Fig. 1a), whereas methylphenidate produced significantly higher increases in heart rate than MDMA ($p < 0.01$; Fig. 1b). This resulted in similar rate-pressure products (systolic blood pressure \times heart rate) for methylphenidate or MDMA, indicating that the total haemodynamic responses to the doses of methylphenidate or MDMA used in the present study were comparable (Table 1). Co-administration of methylphenidate and MDMA produced similar systolic peak pressure increases as MDMA alone (Fig. 1a) and similar peak increases in heart rate as methylphenidate alone (Fig. 1b). However, the rate-pressure product was significantly higher for methylphenidate-MDMA co-administration compared with either MDMA or methylphenidate alone (both $p < 0.001$, Table 1). Methylphenidate, MDMA and the combination all significantly increased body temperature to

Table 1. Mean±S.E.M. values and statistics of pharmacodynamic changes

		Placebo– placebo (mean±S.E.M.)	Methylphenidate– placebo (mean±S.E.M.)	Placebo–MDMA (mean±S.E.M.)	Methylphenidate– MDMA (mean±S.E.M.)	MDMA		Methylphenidate		Methylphenidate× MDMA	
						F _{1,15}	P=	F _{1,15}	p=	F _{1,15}	p=
<i>Subjective effects</i>											
Visual Analogue Scale (VAS, %max)											
Any drug effect	ΔE_{\max}	2.8±1.9	48.9±8.3*** ###	78.0±7.3***	76.9±8.0***	107.65	<0.001	10.87	0.005	36.57	<0.001
Drug liking	ΔE_{\max}	1.4±1.4	50.0±7.9*** ##	80.2±6.8***	73.5±8.3***	81.52	<0.001	12.58	0.003	40.62	<0.001
Drug high	ΔE_{\max}	1.1±0.9	45.8±8.4*** ##	76.6±7.7***	66.1±8.6***	58.72	<0.001	7.45	0.016	26.68	<0.001
Stimulated	ΔE_{\max}	0.8±0.6	53.2±9.0*** #	75.5±8.2***	77.1±8.0***	64.89	<0.001	21.28	<0.001	30.75	<0.001
Happy	ΔE_{\max}	1.5±1.2	12.5±3.4###	34.9±4.6***	24.5±4.3***	48.70	<0.001	0.01	0.940	12.39	0.003
Close to others	ΔE_{\max}	0.4±0.3	9.9±2.9##	29.4±4.8***	23.4±5.0**	35.37	<0.001	0.36	0.556	5.24	0.037
Adjective Mood Rating Scale (AMRS score)											
Emotional excitation	ΔE_{\max}	-0.8±0.5	6.3±1.6***	3.7±1.5*	5.9±1.4***	2.58	0.129	23.50	<0.001	4.66	0.047
Well-being	ΔE_{\max}	0.3±0.7	1.4±0.5#	5.6±1.3*	4.9±1.6*	10.85	0.005	0.01	0.929	0.31	0.584
Extroversion	ΔE_{\max}	-0.4±0.3	1.4±0.5	2.5±0.7**	2.5±0.7**	12.08	0.003	2.35	0.146	2.51	0.134
Activity	ΔE_{\max}	-0.1±0.4	3.3±0.4***	1.8±0.7	2.1±0.7*	0.41	0.531	10.73	0.005	6.84	0.019
Concentration	ΔE_{\max}	-0.1±0.3	2.6±0.4***###	-0.4±0.6	1.6±0.6#	1.38	0.258	31.30	<0.001	0.88	0.362
Anger	ΔE_{\max}	0.3±0.2	0.9±0.3	0.3±0.4	0.8±0.3	0.01	0.935	4.01	0.064	0.01	0.910
Addiction Research Center Inventory (ARCI score)											
Amphetamine group	ΔE_{\max}	1.25±0.2	4.31±0.6***	4.88±0.6***	5.19±0.6***	21.13	<0.001	16.30	<0.001	11.27	0.004
Benzedrine group	ΔE_{\max}	0.63±0.3	3.06±0.6**	1.75±0.6	1.88±0.5	0.00	0.960	11.43	0.004	6.01	0.027
Morphine-benzedrine group	ΔE_{\max}	1.13±0.4	3.56±0.8###	8.63±1.1***	7.75±0.9***	31.97	<0.001	1.36	0.260	6.28	0.024
Phenobarbital-alcohol group	ΔE_{\max}	1.25±0.4	0.81±0.6	2.88±0.7	3.13±0.8	10.85	0.005	0.02	0.891	0.32	0.580
LSD group	ΔE_{\max}	0.0±0.1	1.69±0.6*	2.00±0.5*	2.31±0.5**	15.94	0.001	5.65	0.031	2.91	0.108
Altered State of Consciousness Scale (ASC score)											
Oceanic boundlessness		0.0±0.0	161.6±103.6##	664.9±150.8***	517.6±145.9**	27.86	<0.001	0.01	0.922	2.34	0.147
Anxious ego dissolution		0.5±0.5	86.1±33.1	201.8±87.0*	248.8±87.5**	6.01	0.027	10.04	0.006	0.92	0.352
Visionary restructuralization		0.0±0.0	49.5±29.6	199.8±73.1*	192.9±80.31*	8.50	0.011	0.54	0.476	0.61	0.448
All		0.4±0.4	297.2±161.6##	1066.4±272.7***	959.3±291.4***	20.50	<0.001	0.51	0.488	1.83	0.196
<i>Emotion recognition</i>											
Facial emotion recognition task (accuracy)											
Neutral	% correct	72.50±5.04	70.00±4.83	70.63±6.49	71.25±4.37	0.01	0.932	0.05	0.823	0.17	0.690
Happy	% correct	67.03±2.88	72.97±2.82	71.25±3.82	63.13±3.43#	2.59	0.129	0.28	0.605	20.08	<0.001
Sad	% correct	53.28±4.26	62.66±3.11*###	46.41±4.44	51.72±3.84	11.21	0.004	15.52	0.001	1.12	0.307
Anger	% correct	64.53±3.16	67.81±3.04	61.41±3.89	58.13±4.80	9.09	0.009	0.00	1.000	2.94	0.107
Fear	% correct	56.72±2.65	65.31±2.62*###	49.38±4.17	49.38±3.98	14.50	0.002	4.95	0.042	13.50	0.002
All	% correct	62.81±1.46	67.75±1.57*###	59.81±2.53	58.72±2.48*	13.07	0.003	3.87	0.068	12.73	0.003

Autonomic effect																			
Systolic blood pressure (mm Hg)	E_{\max}	131.6±3.7	146.8±2.2*** ##	154.9±3.4***	158.9±2.9***	55.78	<0.001	19.76	<0.001	12.90	0.003								
Diastolic blood pressure (mm Hg)	E_{\max}	78.9±2.5	90.0±1.8***	94.8±2.8***	94.8±1.6***	33.44	<0.001	17.04	<0.001	10.02	0.006								
Heart rate (beats/min)	E_{\max}	80.7±3.1	103.5±4.1*** ##	93.5±4.3***	107.6±4.6*** ###	8.90	0.009	52.14	<0.001	6.82	0.020								
Rate pressure product (beats*mmHg/min)	E_{\max}	10'465±666	14'645±546***	13'975±837***	16'318±695*** ###	28.49	<0.001	83.04	<0.001	8.24	0.012								
Body temperature (°C)	ΔE_{\max}	0.40±0.10	0.99±0.13**	0.83±0.11*	0.88±0.11*	2.71	0.121	5.58	0.032	12.22	0.003								
Pupil size (mm)	E_{\max}	6.97±0.18	7.10±0.18###	7.57±0.18***	7.71±0.22***	67.63	<0.001	2.16	0.164	0.01	0.939								
Pupil size after light reflex (mm)	E_{\max}	5.13±0.19	5.13±0.19###	6.94±0.25***	6.79±0.27***	118.25	<0.001	0.29	0.559	0.38	0.546								
List of complaints (LC score)																			
Acute adverse effects	up to 5 h	0.3±0.6	10.4±1.7***	8.9±1.7***	16.6±2.5***##	20.70	<0.001	32.83	<0.001	1.53	0.235								
Sub-acute adverse effects	up to 24 h	-0.6±0.5	6.0±1.5***	3.7±1.5*	10.8±1.7***##	16.63	<0.001	32.02	<0.001	0.08	0.784								
Hormones																			
Cortisol (nmol/l)	ΔE_{\max}	-200.3±33.3	-112.7±44.6###	187.2±28.6***	237.4±38.9***	89.89	<0.001	6.26	0.024	0.41	0.531								
Prolactin (mU/l)	ΔE_{\max}	-226.1±45.8	-237.8±45.4###	487.3±106.4***	343.8±134.6***	24.28	<0.001	2.31	0.149	2.51	0.134								
Circulating catecholamines																			
Epinephrine (nmol/l)	ΔE_{\max}	0.01±0.03	0.22±0.03*##	0.44±0.07***	0.68±0.09***##	46.35	<0.001	17.88	<0.001	0.20	0.659								
Norepinephrine (nmol/l)	ΔE_{\max}	0.07±0.15	0.45±0.17	0.90±0.22**	0.53±0.18	7.19	0.017	0.00	0.973	6.49	0.022								
Dopamine (nmol/l)	ΔE_{\max}	0.05±0.03	-0.11±0.10	0.17±0.09	0.08±0.03	3.88	0.068	3.43	0.084	0.37	0.551								

Values are mean±S.E.M. of 16 subjects. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to placebo-placebo. # $p<0.05$, ## $p<0.01$, ### $p<0.001$ compared to placebo-MDMA.

similar extents ($p<0.01$, 0.05 and 0.05 compared with placebo, respectively; Table 1).

Subjective effects

The combination of methylphenidate and MDMA produced similar effects as MDMA alone in all of the psychometric measures. This means that methylphenidate did not enhance the psychotropic effects of MDMA although it produced partly similar psychoactive effects (Table 1, Fig. 1, and Supplementary Figs S1–3). MDMA produced more pronounced and qualitatively different psychotropic effects than methylphenidate. MDMA increased AMRS ratings of well-being ($p<0.05$) and extroversion ($p<0.01$), whereas methylphenidate did not (Supplementary Fig. S1a and 1b, respectively). In the ARCI, MDMA produced significantly higher Morphine-Benzdrine Group effects (i.e. a measure of euphoria) than methylphenidate ($p<0.001$; Supplementary Fig. S2c). In the VASs, MDMA increased all ratings significantly more than methylphenidate (Supplementary Fig. S3a–f). MDMA increased ratings of happy ($p<0.001$) and close to others ($p<0.001$), whereas methylphenidate did not. MDMA also markedly increased the total score ($p<0.001$), particularly oceanic boundlessness ($p<0.001$), in the 5D-ASC, whereas methylphenidate did not (Table 1). Conversely, methylphenidate but not MDMA or the methylphenidate-MDMA combination increased AMRS ratings of activity ($p<0.001$) and concentration ($p<0.01$; Supplementary Fig. S1d and S1e) and ARCI Benzdrine Group effects (i.e. a measure of intellectual efficiency and energy; $p<0.01$, Supplementary Fig. S2b). In the ARCI, both MDMA and methylphenidate produced similar Amphetamine Group effects (both $p<0.001$ compared with placebo; Supplementary Fig. S2a).

Effects on emotion recognition

Methylphenidate increased identification accuracy for sad and fearful faces, reflected by significant main effects of methylphenidate ($F_{1,15}=15.52$, $p<0.001$ and $F_{1,15}=4.95$, $p<0.05$, respectively) and significant *post-hoc* tests compared with placebo (both $p<0.05$; Table 1). In contrast, MDMA impaired the recognition of negative emotions, including sadness ($F_{1,15}=11.21$, $p<0.01$), anger ($F_{1,15}=9.09$, $p<0.01$) and fear ($F_{1,15}=14.50$, $p<0.002$; Table 1).

Endocrine effects

Peak effects and statistics are shown in Table 1. Methylphenidate had no effects on the plasma levels of cortisol, prolactin or NE, but it increased epinephrine compared with placebo ($p<0.05$). MDMA increased the plasma concentrations of cortisol ($p<0.001$), prolactin ($p<0.001$), epinephrine ($p<0.001$), and NE ($p<0.01$) compared with placebo. Methylphenidate significantly reduced the MDMA-induced increase in NE plasma

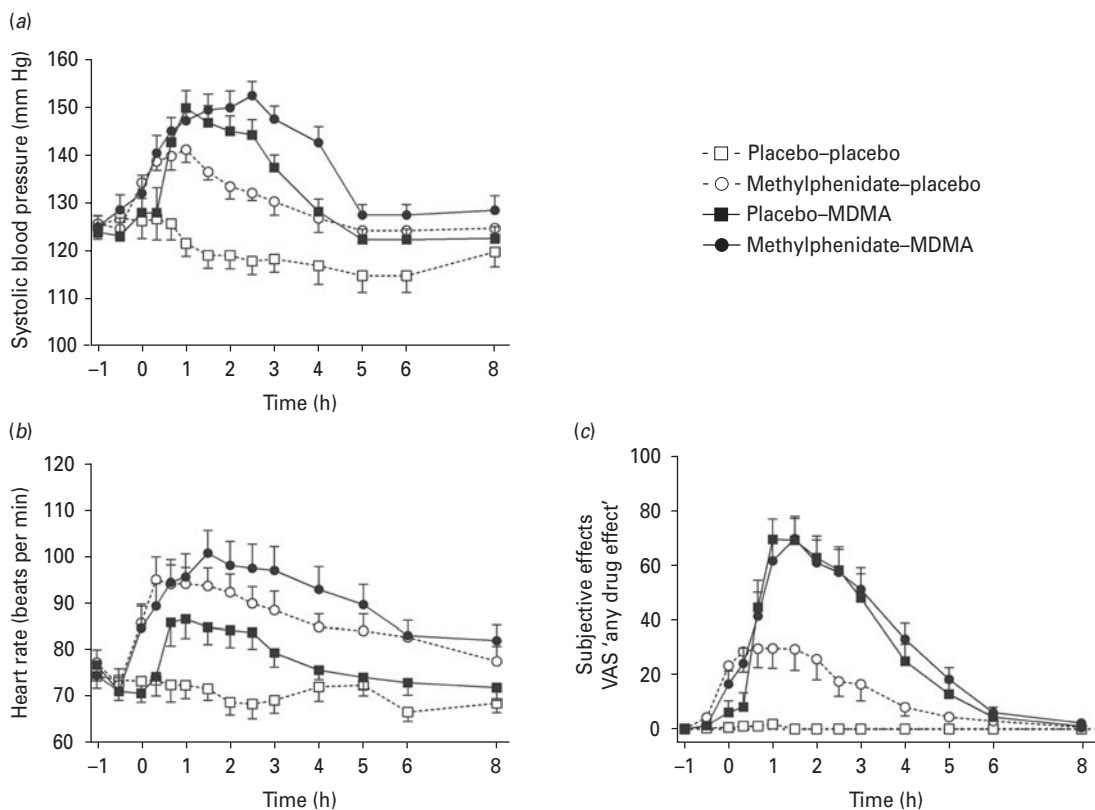


Fig. 1. Pharmacodynamic effects of methylphenidate and MDMA administered alone or in combination. The values are expressed as the mean \pm S.E.M. in 16 subjects. MDMA produced greater increases in systolic blood pressure than methylphenidate (a). Methylphenidate produced greater increases in heart rate than MDMA (b). Co-administration of methylphenidate and MDMA produced similar systolic pressure increases as MDMA alone (a) and similar increases in heart rate as methylphenidate alone (b). However, the rate-pressure product was significantly greater after methylphenidate-MDMA compared with either drug alone (Table 1). (c) Methylphenidate did not enhance the subjective effects of MDMA although methylphenidate produced subjective effects when given alone.

levels ($F_{1,15}$, $p < 0.03$). In contrast, epinephrine concentrations were higher following methylphenidate-MDMA administration compared with either drug alone.

Adverse effects

The values and statistics for adverse effects are shown in Table 1. Both methylphenidate and MDMA produced significant acute (both $p < 0.001$) and sub-acute ($p < 0.001$ and 0.05 , respectively) adverse effects compared with placebo. When methylphenidate and MDMA were co-administered, the total acute and sub-acute adverse effects of both drugs were significantly higher compared with either drug alone ($p < 0.01$ and 0.001 , respectively). Frequently reported acute adverse effects of methylphenidate, MDMA and methylphenidate-MDMA were dry mouth ($n=8$, $n=13$ and $n=15$, respectively), lack of appetite ($n=8$, $n=8$ and $n=16$, respectively), palpitations ($n=8$, $n=4$ and $n=9$, respectively), headache ($n=9$, $n=4$ and $n=7$, respectively), and nausea ($n=7$, $n=1$ and $n=5$, respectively). No severe adverse effects were reported.

Pharmacokinetics

Pharmacokinetic data were missing from one subject, resulting in $n=15$. The pharmacokinetic parameters for all of the drugs and metabolites are shown in Table 2. C_{max} , AUC_{0-24h} and $t_{1/2}$ values for MDMA and its metabolites MDA and HMMA were not altered by the pre-treatment with methylphenidate compared with placebo (Table 2, Fig. 2a, b). However, methylphenidate pre-treatment prolonged the T_{max} of MDMA and MDA compared with placebo ($F_{1,15}=6.79$, $p < 0.02$). CYP2D6 activity influenced MDMA metabolism. Higher CYP2D6 activity (i.e. lower dextromethorphan/dextrorphan urine concentration ratios) correlated with lower MDMA AUC_{0-24h} values ($r_s=0.53$, $p < 0.04$) and higher HMMA C_{max} and AUC_{0-24h} values ($r_s < -0.61$, $p < 0.02$, and $r_s < -0.57$, $p < 0.03$, respectively). The pharmacokinetic-pharmacodynamic relationships for the haemodynamic and psychotropic effects of methylphenidate and MDMA are shown in Fig. 2c, d, respectively. The effects of MDMA showed marked clockwise hysteresis, with substantially smaller dynamic effects at a given plasma MDMA concentration later in time, suggesting rapid

Table 2. Pharmacokinetic parameters of MDMA, MDA, HMMA, and methylphenidate

	C_{\max} (ng/ml)	AUC_{0-24} (ng/ml-h)	$AUC_{0-\infty}$ (ng/ml-h)	$t_{1/2}$ (h)	t_{\max} (h)
MDMA					
Placebo-MDMA	220.1±16.1	2649.4±208.7	3033.9±252.4	7.7±0.4	2.4±0.1
Methylphenidate-MDMA	212.4±9.9	2735.3±166.3	3215.0±256.5	7.7±0.7	3.5±0.4*
MDA					
Placebo-MDMA	11.2±0.8	182.3±13.3	294.1±20.8	16.1±1.3	6.5±0.2
Methylphenidate-MDMA	10.8±0.7	176.1±14.4	310.2±53.4	16.5±2.7	7.4±0.2*
HMMA					
Placebo-MDMA	78.7±40.0	1016.1±116.1	1275.2±154.4	9.7±0.7	3.6±0.3
Methylphenidate-MDMA	69.1±7.7	973.9±96.4	1259.4±143.8	10.2±1.0	4.2±0.4
Methylphenidate					
Methylphenidate-placebo	30.4±2.4	175.4±14.0	–	2.8±0.1	2.3±0.2
Methylphenidate-MDMA	30.6±2.7	175.2±14.7	–	2.8±0.1	2.4±0.2

Values are mean±S.E.M. of 15 healthy subjects. C_{\max} , maximum plasma concentration; T_{\max} , time to maximum plasma concentration; AUC, area under the plasma concentration–time curve. * $p < 0.05$ compared to placebo-MDMA.

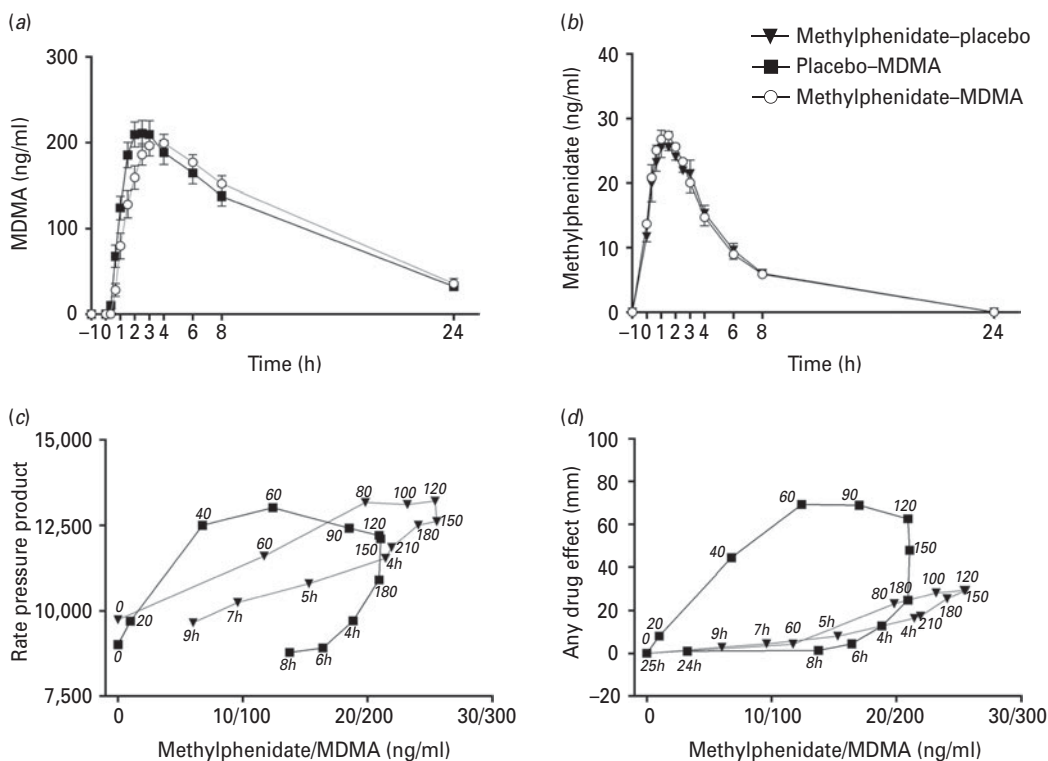


Fig. 2. Pharmacokinetic plasma concentration–time profiles of MDMA (a) and methylphenidate (b). The values are expressed as the mean±S.E.M. in 15 subjects. Methylphenidate had no effect on the C_{\max} or AUC values of MDMA. Methylphenidate pretreatment increased the T_{\max} of MDMA compared with placebo pretreatment. The pharmacodynamic haemodynamic (c) and psychotropic (d) effects of MDMA and methylphenidate are plotted against the plasma concentrations of MDMA and methylphenidate. The values are expressed as the means of 15 subjects, with S.E.M. omitted for clarity. The time of sampling is noted next to each point in minutes or hours after MDMA or methylphenidate administration, respectively. The effects of MDMA decreased over time, despite high plasma concentrations, resulting in more pronounced clockwise hysteresis in the effect–concentration plot of MDMA compared with methylphenidate. The clockwise hysteresis indicates acute pharmacological tolerance to MDMA but not methylphenidate.

acute pharmacological tolerance. In contrast, the effect–concentration plots of methylphenidate showed little hysteresis, consistent with no relevant acute pharmacological tolerance.

Discussion

Methylphenidate did not attenuate the pharmacodynamics effects of MDMA as we originally hypothesized

it should. However, methylphenidate did not enhance any of the psychotropic effects of MDMA, although methylphenidate produced considerable subjective effects on its own. The thermogenic effect of methylphenidate–MDMA was also similar to both drugs alone. In contrast, the haemodynamic response to methylphenidate–MDMA was significantly higher compared with MDMA or methylphenidate alone. Methylphenidate–MDMA also resulted in more subjective adverse effects and higher plasma epinephrine concentrations than either drug alone. From a safety or recreational use perspective, the findings overall indicate that the combined use of methylphenidate and MDMA would not result in additional psychoactive effects compared with MDMA alone, but such a combination would enhance cardiovascular and adverse effects. No previous studies have assessed methylphenidate–MDMA interactions. Studies with other psychostimulants showed that maintenance on up to 90 mg methylphenidate either did not alter or increased the cardiostimulant effects of cocaine and decreased some of its positive subjective effects (Collins et al., 2006; Winhusen et al., 2006).

The interactive effects of methylphenidate and MDMA are pharmacodynamic in nature and are not explained by pharmacokinetic interactions, as documented in the present study. MDMA is mostly metabolized by *O*-demethylation by CYP2D6 to 3,4-dihydromethamphetamine (de la Torre et al., 2012). A minor pathway of MDMA includes *N*-demethylation by CYP2B6 and CYP3A4 to the active metabolite MDA. In the present study, methylphenidate did not alter the C_{max} , AUC or $t_{1/2}$ values of MDMA, MDA or HMMA, indicating that methylphenidate has no effects on MDMA metabolism. However, methylphenidate increased the T_{max} of MDMA and MDA, suggesting the delayed absorption of MDMA. Conversely, MDMA did not alter the pharmacokinetics of methylphenidate, which is metabolized by carboxylesterase 1 to inactive ritalinic acid (Sun et al., 2004).

A major limitation of the study is the lack of a dose–response design. We used only single, mid- to high-doses of methylphenidate and MDMA. A more complete characterization of the methylphenidate–MDMA interaction would require testing different doses of both drugs.

Our findings are consistent with the view that DAT does not critically contribute to the effects of MDMA in humans. In similar studies in healthy subjects, the psychotropic and autonomic effects of MDMA were reduced by selective SERT inhibition (Liechti et al., 2000; Liechti and Vollenweider, 2000) and NET inhibition (Hysek et al., 2011) and almost completely blocked by combined SERT/NET inhibition (Hysek et al., 2012d). In monkeys, a selective DAT inhibitor and methylphenidate did not alter the acute behavioural or cognitive effects of MDMA (Verrico et al., 2008; Fantegrossi et al., 2009). In contrast, the dual DAT/NET inhibitor bupropion reduced the acute subjective effects of methamphetamine in humans (Newton et al., 2006). It remains to be tested

whether bupropion alters the acute response to MDMA in humans. Overall, the available data indicate that the SERT and NET mediate most of the acute effects of MDMA, but the role of DA remains unclear.

The present study directly compared the acute clinical pharmacological effects of methylphenidate and MDMA. The doses of the drugs used in the present study resulted in comparable overall haemodynamic responses, reflected by similar rate–pressure products. MDMA produced greater increases in blood pressure compared with methylphenidate. Methylphenidate led to greater increases in heart rate compared with MDMA. The thermogenic response to the combination of methylphenidate–MDMA was similar to the response to either methylphenidate or MDMA alone. The finding indicates that concomitant methylphenidate does not enhance the risk of MDMA-induced hyperthermia.

Both methylphenidate and MDMA produced similar subjective Amphetamine Group effects in the ARCI. However, MDMA produced more ‘empathogenic’ mood effects than methylphenidate, including higher VASs for drug liking, happiness and closeness to others, and AMRS scores for well-being and euphoria. MDMA but not methylphenidate also produced psychedelic and mind-altering effects in the 5D-ASC. In contrast, methylphenidate but not MDMA enhanced concentration and activity in the AMRS and produced Benzadrine Group effects in the ARCI, consistent with higher self-rated intellectual efficiency and energy (Martin et al., 1971) and its use as a cognitive enhancer (McCabe et al., 2005).

An additional novel finding of the present study is that methylphenidate enhanced the recognition of fearful and sad faces. Thus, methylphenidate tended to produce negative bias in emotional information processing, similar to the DA/NE releaser D-amphetamine (Hariri et al., 2002; Wardle et al., 2012). MDMA, in contrast, produced positive bias, as previously reported (Bedi et al., 2010; Hysek et al., 2012a), and similar to the 5-HT agonist psilocybin (Kometer et al., 2012). Thus, although methylphenidate and MDMA share some amphetamine-type effects, their effects on the processing of emotional information are very different. The positive bias in emotion processing induced by MDMA likely enhances social interaction. In contrast, a negative bias in emotion processing is observed in patients with depression (Bourke et al., 2010). Enhanced recognition of negative emotions may contribute to negative drug reactions and psychosis during methylphenidate treatment, particularly in a negative social environment and when higher doses are used (Ross, 2006). The effects of methylphenidate on socio-emotional cognition should be investigated further because of its widespread use for the treatment of attention-deficit/hyperactivity disorder and as a cognitive enhancer.

Cortisol and prolactin are markers of serotonergic activity (Sommers et al., 1994; Seifritz et al., 1996). MDMA but not methylphenidate increased plasma cortisol and

prolactin concentrations as expected (Weizman et al., 1987; Upadhyaya et al., 2003; Dumont and Verkes, 2006). Methylphenidate did not alter MDMA-induced increases in circulating cortisol or prolactin. MDMA increased plasma NE levels. Plasma NE mostly represents an overflow of NE from sympathetic nerves into the circulation (Eisenhofer et al., 1995). Methylphenidate reduced the MDMA-induced increase in plasma NE, suggesting that the pharmacodynamic interactive effects of methylphenidate and MDMA are partially attributable to a pharmacological interaction at the NET. Both methylphenidate and MDMA increased plasma epinephrine levels, and the effect was significantly greater when both drugs were administered together. Circulating epinephrine is mainly derived from the adrenals (Eisenhofer et al., 1995) and is a marker of the central stimulation of DA (Volkow et al., 2003), NE (Kuczenski and Segal, 1997) and 5-HT (Blardi et al., 2005). Epinephrine lowers peripheral resistance, resulting in an increase in heart rate. In contrast, NE increases peripheral resistance, resulting in an increase in blood pressure and a decrease in heart rate (Allwood et al., 1963). Thus, the different effects of methylphenidate and MDMA on heart rate and blood pressure are consistent with their plasma catecholamine releasing profiles.

Plotting the pharmacokinetic–pharmacodynamic relationships for MDMA and methylphenidate revealed a clinically important difference between the two drugs. Rapid acute pharmacodynamic tolerance was observed to the effects of MDMA but not methylphenidate. Despite the long plasma half-life of MDMA (i.e. 8 h) and persistent high drug levels in the blood, most pharmacodynamic drug effects rapidly return to baseline within 4–6 h. In contrast, the dynamic effects of methylphenidate closely reflected the plasma concentrations of methylphenidate and are consistent with the plasma half-life of 3 h. Thus, in the case of MDMA, a long plasma half-life does not necessarily mean that the actual drug effects are also long-lasting. The acute tolerance to MDMA likely reflects its mode of action resulting in a functional depletion of presynaptic monoamine stores so that no more transmitter can be released, despite high concentrations of MDMA.

In conclusion, co-administration of methylphenidate and MDMA produced pharmacodynamic effects that were not substantially larger than those of MDMA alone. No relevant pharmacokinetic interactions between methylphenidate and MDMA were observed. The effects of MDMA but not methylphenidate were characterized by acute pharmacodynamic tolerance. Finally, MDMA produced positive emotional bias and methylphenidate produced negative emotional bias in emotion recognition, and this requires further investigation.

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Statement of Interest

None.

Supplementary material

For supplementary material accompanying this paper, visit <http://dx.doi.org/10.1017/S1461145713001132>

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