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Pharmacology, Biochemistry and Behavior 83 (2006) 47 – 55
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Memantine increases cardiovascular but not behavioral effects of cocaine in methadone-maintained humans

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Received 10 August 2005; received in revised form 2 November 2005; accepted 6 December 2005
Available online 30 January 2006

Abstract

Previous work has suggested that maintenance on the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist, memantine, increased the subjective effects of smoked cocaine in experienced cocaine users. To determine whether this phenomenon occurs in opioid-dependent individuals, eight (seven male, one female) methadone-maintained cocaine smokers participated in a 47-day inpatient and outpatient study to assess the effects of memantine on smoked cocaine self-administration, subjective effects, and cardiovascular responses. The participants were maintained on memantine (0 mg and 20 mg daily) for 7–10 days prior to laboratory testing, using a double-blind crossover design. Under each medication condition during inpatient phases, participants smoked a sample dose of cocaine base (0, 12, 25, and 50 mg) once, and were subsequently given five choice opportunities, 14 min apart, to self-administer that dose of cocaine or receive a merchandise voucher (US$5.00). Each cocaine dose was tested twice under each medication condition, and the order of medication condition and cocaine dose were varied systematically. Memantine maintenance did not alter the subjective or reinforcing effects of cocaine. Several cardiovascular responses, however, including peak and initial diastolic pressures following cocaine, were significantly greater during memantine maintenance, although these elevations were not clinically significant. Taken together, these findings corroborate earlier data suggesting that this dose of memantine will not be helpful in the pharmacotherapy of cocaine abuse.

Keywords: Cocaine; Memantine; NMDA antagonist; Methadone; Self-administration; Subjective effects; Cardiovascular effects

1. Introduction

A potentially promising approach to identifying medications for the treatment of cocaine dependence is to study groups of cocaine abusers sharing certain characteristics, such as a common co-morbid substance use disorder or psychiatric illness (Kosten and Sofuoglu, 2004). These populations may respond more robustly to targeted pharmacotherapies and consequently shed light on new avenues for pharmacological treatments (Albanese et al., 2000). One group of cocaine users meriting special attention is the population of methadone-maintained cocaine smokers.

Cocaine use among methadone patients is a significant problem (Bovasso and Cacciola, 2003; Hartel et al., 1995; Hser et al., 1998; Silverman et al., 2004), and it may increase following entry into methadone maintenance treatment (Chaisson et al., 1989). Notably, cocaine use is independently associated with both increased heroin use among methadone-maintained patients (Hartel et al., 1995) and with increased rates of HIV seroprevalence among IV drug abusers (Chaisson et al., 1989; Silverman et al., 2004). In addition, cocaine produces greater effects when given to patients maintained on methadone, who report larger responses on measures of "positive" effects of cocaine compared with experienced opioid abusers currently abstinent from opioids (Preston et al., 1996). The phenomenon is dose-dependent, as research volunteers maintained on methadone above 60 mg/day reported greater cocaine effects than those treated with smaller methadone doses (Foltin et al., 1995a).

There have been numerous promising preclinical findings for NMDA antagonists as potential medications for cocaine dependence (Bespalov et al., 2000; Brackett et al., 2000;

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doi:10.1016/j.pbb.2005.12.003

Hyytiä et al., 1999; Karler and Calder, 1992; Pap and Bradberry, 1995; Pulvirenti et al., 1991; Schenk et al., 1993; Sripada et al., 1998; Witkin et al., 1999), although a prior study from this laboratory showed that the NMDA antagonist, memantine, increased some "positive" subjective effects of cocaine among cocaine smokers (Collins et al., 1998). Given an extensive literature suggesting that NMDA antagonists may both prevent the development of opioid tolerance and attenuate established mu opioid tolerance (Danysz et al., 2005; Elliott et al., 1994a,b, 1995; Popik and Danysz, 1997; Trujillo, 1995; Trujillo and Akil, 1991, 1994), it seemed likely that memantine maintenance would produce different effects in methadone-maintained individuals. Also, the possibility of an important interaction between memantine and methadone exists because the D-isomer of methadone, D-methadone, itself has modest NMDA antagonist effects (Inturrisi, 1994, 2002), suggesting the possibility of synergistic antagonism at the NMDA receptor for individuals maintained on both medications. Whether the combination of memantine and methadone would increase or decrease the behavioral effects of cocaine was therefore explored. As the use of NMDA antagonists among methadone-maintained individuals has not previously been reported, it was important to observe the interactions of methadone and memantine in a controlled setting. The present study examined the effects of memantine on smoked cocaine self-administration and cocaine subjective effects in a population of methadone-maintained cocaine smokers. The 20 mg dose was chosen because it has been safely used in prior research by this group (Collins et al., 1998), and is the standard dose for Alzheimer's disease, ensuring that findings would be relevant to the clinical literature.

2. Methods

2.1. Participants

Eight methadone-maintained research volunteers, seven male (four hispanic and three white) and one female (white), 27–42 years of age (mean=37), who were not seeking treatment for their cocaine smoking, were solicited through word-of-mouth referral and newspaper advertisements in New York, NY. Daily methadone dosages for these individuals ranged from 70 mg to 100 mg (mean 86.3 mg/day). The research participants weighed between 56.8 kg and 81.8 kg (mean=74.8 kg). They reported using cocaine for 16.6±5.5 years and spending US$273±147 per week on cocaine (the current cost of cocaine on the street is US$30–40 per gram). Only 3 of the 8 reported using street heroin, spending between US$10 and US$40 weekly (mean=US$22/week). All 8 participants also smoked tobacco cigarettes (mean of 14 cigarettes daily; range 2.5–20 cigarettes/day). The participants had completed 13.3 years of education (range 10–19 years).

All participants passed medical and psychological evaluation prior to the study, and none were receiving psychiatric treatment. Each participant signed a consent form, approved by the Institutional Review Boards of the College of Physicians and Surgeons of Columbia University and The New York State Psychiatric Institute. Six additional participants (1 black female, 3 Hispanic males, 1 white male, and 1 Asian male) began the protocol but did not complete it. Of these, one male was unable to comply with the study protocol. Another male was dropped from the protocol because he displayed premature ventricular contractions (PVCs) during a laboratory cocaine administration session. The others ended their participation for various personal reasons.

2.2. Procedure

The apparatus and laboratory set-up were as previously described (Collins et al., 1998; Foltin et al., 1995b; Haney et al., 1999). The first two participants were admitted to the Irving Center for Clinical Research in the New York Presbyterian Hospital for the entire 47-day study. Participants had access to television, radio, and videotape movies while on the Clinical Research Center, but they were allowed no visitors and no passes off the unit. Because of our concern for the possibility that memantine would attenuate established opioid tolerance, the inpatient stay allowed a careful evaluation of the effects of memantine in combination with methadone (as well as cocaine) prior to providing subsequent participants with memantine on an outpatient basis. The remaining six participants were alternately inpatients and outpatients over 47 days, which included a total of 21 inpatient days (Fig. 1). In this alternating inpatient and outpatient design, participants were first admitted to the research center for 2 days when the experimental medication (memantine or placebo) was initiated. They were subsequently followed outpatient for 8 days, admitted for 10 days (which included 2–3 days before the laboratory sessions as well as the initiation of the crossover medication condition), followed outpatient for 11 days, admitted again for 9 days (which again included 2–3 days before the laboratory sessions), and followed outpatient for 7 days. During the outpatient phases of the study, each individual was seen every Monday, Wednesday, and Friday, at which time he or she was monitored for the emergence of side effects and/or other adverse reactions. An observed urine was collected for drug screening. Attendance at outpatient visits was reinforced with US$25 in cash, in part to offset the expenses incurred travelling to and spending time in the laboratory. An additional US$25 for each outpatient visit was paid upon completion of the study.

To assess whether memantine might decrease cocaine use in combination with behavioral interventions, research volunteers were offered US$25 in merchandise vouchers, redeemable at local merchants, for each cocaine-free urine submitted during outpatient phases. This design parallels the earlier study of memantine maintenance in cocaine smokers (Collins et al., 1998).

While inpatient, all individuals participated in a total of sixteen 2.5-h weekday laboratory sessions, two per day on 4 days between study days 14 and 18, and two per day on 4 days between study days 35 and 39. Individuals were exposed to each dose of cocaine (0, 12, 25 and 50 mg) twice during each memantine maintenance condition. Dose order during the laboratory sessions was as follows: the four available cocaine

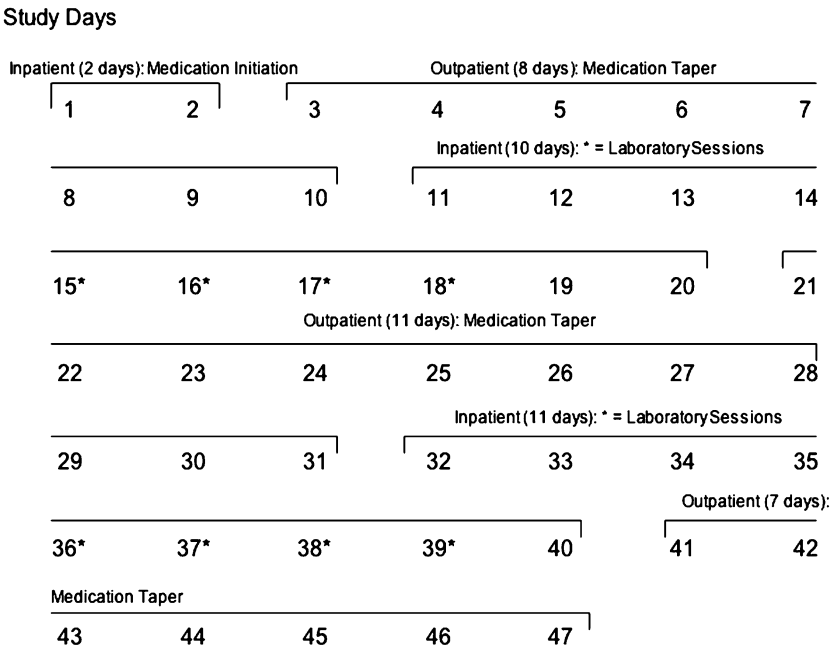

Fig. 1. The 47-day inpatient/outpatient study design.

doses were initially tested in four consecutive lab sessions over 2 days, with cocaine doses presented in random order, except that, to reduce research risk, no participant received the highest cocaine dose during his first laboratory session of the study. The four doses were then again tested in four consecutive sessions over two of the remaining three weekdays, so that doses given in the morning at the beginning of the week were given in the afternoon at the end of the week. This counterbalanced design reduced the likelihood that time of day factors, including carry-over effects from morning to afternoon sessions, would confound the results, and controlled for variability related to time of methadone dosing. Laboratory sessions began at approximately 9:30 AM and 1:30 PM. Cocaine dosing occurred between approximately 10:00 AM and 11:30 AM and again between 2:00 PM and 3:30 PM.

Participants were maintained on memantine, 20 mg daily, and placebo, for 7–10 days prior to the laboratory testing periods. Five of the eight participants received memantine first, and the remaining three received placebo first. Research participants, all nursing staff and the investigators (with the exception of ASW, who did not have direct contact with the participants after screening) were blind to the medication condition throughout the study. Methadone dosing (administered as 5 mg tablets) occurred at 8 AM daily.

During laboratory sessions, research nurses located in an adjacent room continuously observed participants via a one-way mirror, and the participants and staff could communicate via an intercom system. In each of the 16 laboratory cocaine self-administration sessions, there was a 20-min period of baseline vital sign observations and mood scales (see description below). Following the baseline assessments, research participants were allowed to "sample" the dose of cocaine base (0, 12, 25 and 50 mg) available that session. Cocaine smoking was accomplished by placing the metered dose of cocaine base in an 8 cm glass tube, or "stem," packed with fine metal mesh, blindfolding the participant, and allowing him or her to hold the glass stem while the research nurse held the flame from the lighter until the individual had finished inhaling the smoke. Following the sample dose, participants were given five choice trials, spaced 14 min apart, when they could choose to smoke the same dose of cocaine as in the sample dose or to receive a merchandise voucher worth US$5.00.

Choice trials were signaled by an audible computer-generated tone and the appearance in outline form of two squares (3 cm × 3 cm) on the computer monitor. Participants selected an option by moving the cursor to the left or right (illuminating the square associated with that position), and pressing a button on the mouse 200 times. Once the response requirement was completed, the message "Left (or Right) Option Chosen" appeared at the bottom of the screen. A cocaine dose or voucher was only given on trials in which cardiovascular activity was within our criteria for safe drug administration (i.e. HR < 130, DP < 100, SP < 165) at the three vital signs measurements taken at 4 min, 2 min and 0 min prior to the scheduled reinforcer administration.

2.3. Subjective-effects questionnaires

A subjective effects battery was completed during laboratory sessions at baseline, 4 min following each dose of cocaine or voucher, and 30 min following the last dose of cocaine or voucher. The battery consisted of a series of 10-cm visual analog scales (VAS). Eighteen of these VAS were labeled "I feel. . ." "Stimulated," "High," "Anxious," "Sedated," "Depressed," "Hungry," "Friendly," "Miserable," "On edge," "Alert," "Tired," "Talkative," "Self-confident," "Social," "Irritable," "Confused," "Good Drug Effect," and "Bad Drug Effect." Four VAS were used to operationalize drug craving and

were labeled "I want. . ." "Cocaine," "Heroin," "Ethanol," and "Nicotine." Three VAS were related specifically to the cocaine dose the participant had just received and were labeled "The choice was of high quality," "The choice was potent," and "I liked the choice." A final question asked individuals "How much would you pay for the dose you just received?"

To assess for the possible interactions (i.e., attenuation of opioid tolerance) of memantine and methadone, the research participants completed a modified version of the Opiate Symptom Checklist (the "other" item was omitted; Foltin and Fischman, 1992; Fraser et al., 1961; Martin and Fraser, 1961), the Subjective Opiate Withdrawal Scale (SOWS; Handelsman et al., 1987) and the Objective Opiate Withdrawal Scale (OOWS; Handelsman et al., 1987) each day during the inpatient phases of the protocol. The OOWS and SOWS were completed each morning prior to that day's methadone dose. The modified Opiate Symptom Checklist was completed each afternoon at approximately 6:00 PM.

2.4. Serum analyses

In order to monitor compliance with the outpatient medication regimen, memantine levels were assessed in weekly bloods drawn during laboratory visits during outpatient phases of the study. These blood samples were assayed for memantine levels by a liquid chromatographic procedure using fluorescence detection (Suckow et al., 1999). All laboratory analyses were carried out by the Analytical Toxicology Laboratory at Rockland State Psychiatric Center.

2.5. Drugs

Cocaine hydrochloride (provided by The National Institute on Drug Abuse) was prepared as described previously (Foltin et al., 1990). Memantine (in 0 mg, 5 mg, and 10 mg tablets, Merz & Co., Frankfurt, Germany) was administered as two identical tablets at 8:00 AM each day on the Center for Clinical Research. Methadone was administered in 5 mg tablets at 8:00 AM during inpatient phases. Participants returned to their methadone programs during outpatient phases for continued methadone dosing. During outpatient phases, participants were given memantine at approximately 10:00 AM by the research nurse on Mondays, Wednesdays, and Fridays, and they were given one (Monday and Wednesday) or two (Friday) packets of medication to be taken between visits. Each medication packet contained two identical tablets and was labeled with the participant's name, date, and scheduled dosing time. Memantine was administered once a day in order to facilitate compliance. Participants were required to return the medication packaging, whether or not the medication had been taken.

Memantine was tapered up to 20 mg and down to 0 mg over 6 days. In humans, memantine is eliminated in a multi-compartment model (Merz & Co.) and the contribution of the first phase to drug action is considerably greater than that of the terminal phase (Merz & Co.). Although the half-life for the terminal elimination phase is between 59 and 104 h, the half-life for the clinically relevant first phase is 4–9 h, and it is on this relevant first-phase that the clinical dosing recommendations for twice daily dosing in Alzheimer's disease are based (Merz & Co.). This first-phase half-life guided the choice for the duration of the memantine dosing during crossover and maintenance, so that individuals would be at steady-state levels of memantine when tested in the laboratory.

2.6. Data analysis

Data were analyzed using SuperANOVA statistical software for Macintosh. Each scale of the subjective-effects questionnaire was summarized as the maximal score obtained during the session. Maximal rate-pressure product (RPP; heart rate × systolic pressure), an index of myocardial oxygen demand (Holmberg et al., 1971; Kitamura et al., 1972), and HR, SP, DP and mean arterial pressure (MAP) were analyzed. The area under the curve (AUC) from time zero to the end of each laboratory session, determined using Simpson's Rule (Tallarida and Murray, 1981), was also analyzed for each of the cardiovascular measures. Because the number of doses taken over the course of a session varied, a similar analysis was done for the effects of the first dose of cocaine taken. The data were analyzed using a four-factor repeated measures ANOVA with maintenance condition (memantine vs. placebo) as the first factor, cocaine dose (0, 12, 25, 50 mg) as the second factor, replication (first vs. second) of the cocaine dose under each memantine maintenance condition as the third factor, and the order of memantine maintenance (placebo first or memantine first) as the fourth factor. A number of the subjective effects measures showed statistically significant interactions between maintenance condition and the order of active memantine administration, but the pattern was inconsistent among measures, so these effects will not be reported. Post hoc analyses were carried out with means comparisons for differences between memantine and placebo at each specific dose of cocaine.

Active or placebo cocaine was administered on 439 dosing occasions, and was withheld on only 14 occasions (3% of all doses) due to elevated cardiovascular activity (four individuals had at least two doses withheld, always during sessions with either 25 mg or 50 mg cocaine base). When cocaine was not given, participants still completed the subjective-effects measures and cardiovascular monitoring continued. Thus, the data obtained, even though cocaine was not administered, were used in the analyses.

3. Results

3.1. Cardiovascular effects

Fig. 2 shows the effect of cocaine on the cardiovascular responses to the first dose of cocaine during each session as a function of cocaine dose and maintenance condition (panels A through C), and the peak cardiovascular response across all sessions (panels D through F). Cocaine produced dose-dependent increases in first-dose HR (panel A), SP (panel B), DP (panel C), and peak HR, SP, and DP ($p < 0.0001$ for all).

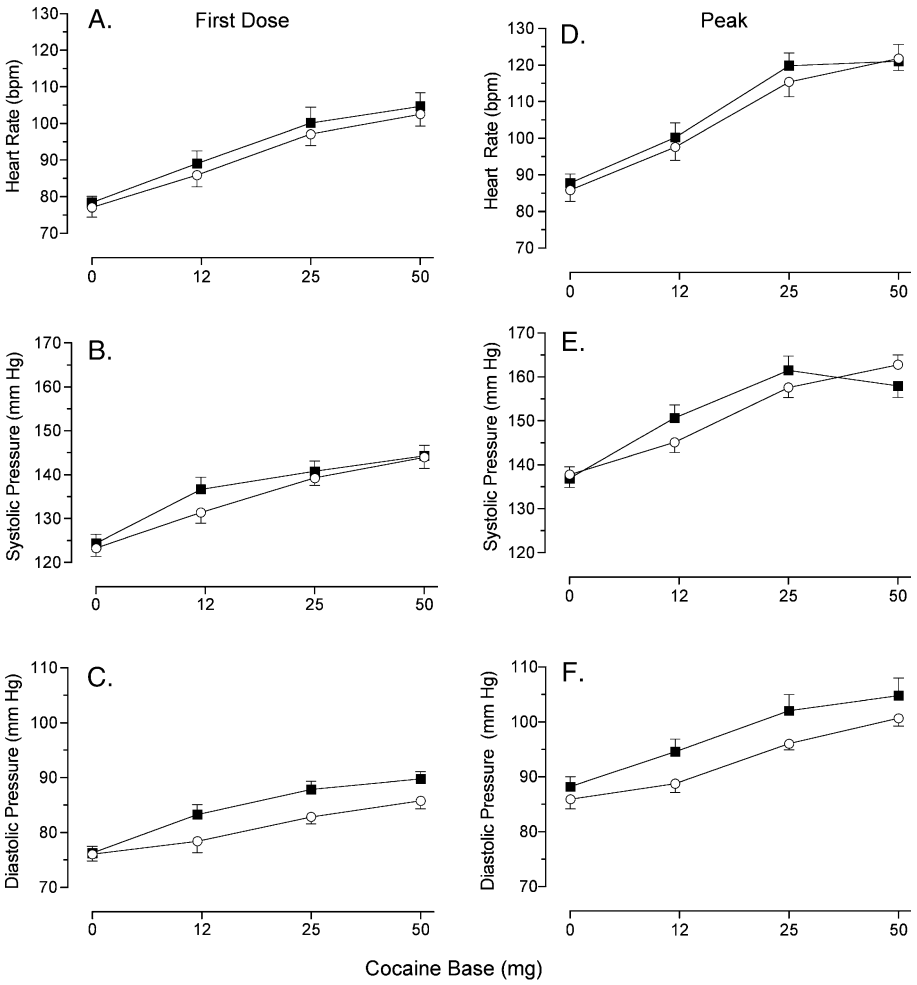

Fig. 2. Mean heart rate (panel A), systolic pressure (panel B), diastolic pressure (panel C) following the first dose of cocaine and mean peak heart rate (panel D), peak systolic blood pressure (panel E), and peak diastolic pressure (panel F) as a function of cocaine dose and maintenance medication condition. Error bars represent ±1 SEM. Overlapping error bars were omitted for clarity.

AUC measures for HR, SP, and DP also showed cocaine dose-dependent increases ($p<0.0001$ for all; data not shown). Neither the replication of cocaine doses during each week nor the order of memantine administration had an effect on the cardiovascular effects of cocaine during the study.

Memantine maintenance was associated with an increase in first-dose DP ($p<0.0113$; Fig. 2, panel C) following cocaine administration. There was also a trend toward a 5 mm Hg increase in cocaine-associated peak DP ($p<0.06$; Fig. 2, panel F) during memantine maintenance. In addition, memantine maintenance produced increases in AUC measures of SP ($p<0.0437$; data not shown) and DP ($p<0.0188$; data not shown).

3.2. Subjective effects

Cocaine produced dose-dependent increases (Fig. 3) in peak ratings of "I feel…" "High," ($p<0.0002$; panel A), "Stimulated," ($p<0.0002$; data not shown), "A good drug effect," ($p<0.0001$; panel C), and "Anxious," ($p<0.0175$; data not shown). There were dose-dependent decreases in peak ratings of "Tired," ($p<0.0067$; not shown). On ratings of the cocaine dose just received, cocaine produced dose-dependent increases in ratings of "The choice was of high quality," ($p<0.0001$; data not shown), "The choice was potent," ($p<0.0001$; data not shown), "I liked the choice," ($p<0.0001$; Fig. 3, panel B), and how much participants were willing to pay for the dose ($p<0.0001$; Fig. 3, panel D). Peak subjective effects ratings of cocaine effects did not differ as a function of medication maintenance condition. Nevertheless, with the exception of the ratings of "I feel anxious," "I feel tired," and "The choice was potent," the subjective effects responses described here constitute a group of "positive" cocaine effects, all of which displayed a non-statistically significant pattern of higher ratings during memantine maintenance. The pattern of subjective effects following the first dose of cocaine (data not shown) was similar to the pattern observed for peak effects. Neither the replication of cocaine doses during each week nor the order of memantine administration had an effect on the subjective effects of cocaine during the study.

Craving for heroin (VAS ratings of "I want heroin") was reduced by approximately 6 mm during memantine maintenance ($p<0.05$), although cocaine craving (ratings of "I want cocaine") was unchanged.

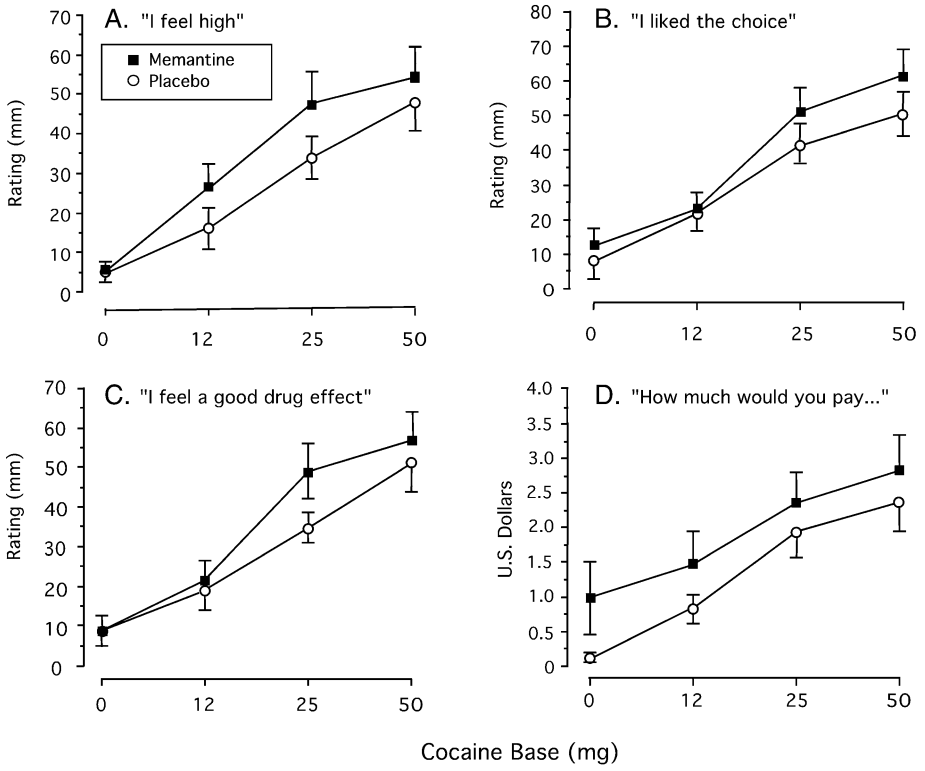

Fig. 3. Mean peak ratings of "I feel high" (panel A), "I liked the choice" (panel B), "I feel a good drug effect" (panel C), and "How much would you pay for the dose you just received?" (panel D). The visual analog scale (VAS) ranged between 0 and 100 mm. The "pay" rating scale ranged from US$0 to US$25. Error bars represent ±1 SEM. Overlapping error bars were omitted for clarity.

There was no evidence of an interaction between memantine maintenance and methadone maintenance. Specifically, opiate effects as assessed by the modified Opiate Symptom Checklist, as well as withdrawal effects assessed by the OOWS and the SOWS, were no different during periods of memantine maintenance compared with periods of placebo maintenance.

3.3. Cocaine choice

Fig. 4 shows the average number of doses of cocaine chosen (maximum five doses available) as a function of cocaine dose and maintenance condition. Active cocaine was chosen significantly more often than placebo cocaine ($p<0.0001$). Overall, memantine maintenance had no effect on the number of times subjects chose cocaine over the alternative reinforcer (US$5.00 voucher), although at the highest cocaine dose (50 mg cocaine base), there was a trend ($p<0.0541$) toward fewer cocaine choices during memantine maintenance.

3.4. Outpatient urine toxicology

There was no effect of memantine during the outpatient phases of this study on the number of urine samples positive for cocaine. During outpatient memantine maintenance, individuals submitted 24 urine samples with 17/24 (71%) positive for cocaine. During outpatient placebo maintenance, individuals submitted 30 urine samples with 23/30 (77%) positive for cocaine.

3.5. Serum analyses

There were no differences in cocaine levels as a function of memantine maintenance condition. During outpatient phases of the protocol, the mean levels of memantine during both dosage escalation and taper were 37±15 ng/mL. There was residual memantine ranging between 0 ng/mL and 8 ng/mL during outpatient phases in individuals who had begun on memantine and were taking placebo during the middle outpatient phase of the study.

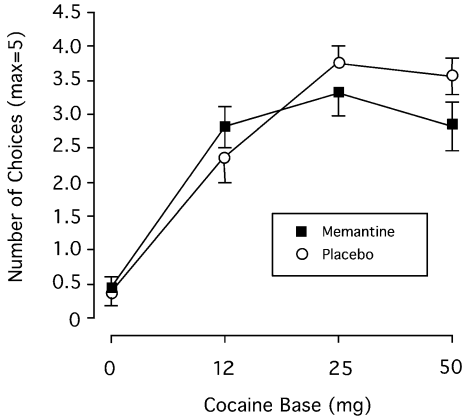

Fig. 4. Mean number of cocaine choices (maximum=5) as a function of cocaine dose and maintenance medication condition. Error bars represent ±1 SEM. Overlapping error bars were omitted for clarity.

4. Discussion

In the present study, maintenance on memantine (20 mg daily) for a period of 7–10 days prior to laboratory testing had no effect on the subjective or reinforcing effects of cocaine in a sample of methadone-maintained cocaine smokers. Memantine maintenance was, however, associated with a significant increase in diastolic blood pressure response to cocaine in this population. In addition, ratings of "I want heroin" were significantly lower during memantine maintenance, although there were no other interactions observed between memantine maintenance and methadone. To the best of our knowledge, this is the only study that has examined the effects of memantine in cocaine-dependent, methadone-maintained humans.

An earlier parallel study in non-opioid dependent volunteers (Collins et al., 1998) reported an enhancement of the subjective effects of cocaine during memantine maintenance. A similar or more pronounced effect of memantine was expected for this opioid-dependent population, on two speculative grounds. First, because NMDA antagonists attenuate established mu opioid tolerance (Danysz et al., 2005; Elliott et al., 1994a, b, 1995; Kozela et al., 2003; Wong et al., 1996), memantine could have increased the methadone effect, which would likely increase the subjective effects of cocaine (Foltin et al., 1995a). Second, because the D-isomer of methadone, D-methadone, has NMDA antagonist activity (Inturrisi, 1997, 2002), the combination of memantine and methadone (administered as the racemic mixture of D- and L-methadone) might have produced synergistic antagonism at the NMDA receptor. The possibility that NMDA activity of D-methadone may contribute to the observed enhancement of some cocaine actions in those maintained on methadone (Foltin et al., 1995a; Preston et al., 1996) remains to be tested. Indirect evidence for such an effect comes from an earlier study (Foltin and Fischman, 1996), in which opioid-dependent individuals self-administered cocaine less frequently when maintained on buprenorphine (which lacks NMDA antagonism) compared with methadone. In the present study, there was little evidence of the predicted synergy between methadone and memantine, although the increase in the cardiovascular response to cocaine might reflect such an interaction.

The subjective effects data reveal that the group of "positive" cocaine subjective effects was consistently greater during memantine maintenance, although no individual subjective effect reached statistical significance. This is consistent with the previous findings in non-opioid-dependent individuals (for whom these findings did reach statistical significance. Interestingly, the trend ($p < 0.0541$) toward less self-administration of the highest dose of cocaine during memantine maintenance could be consistent with an enhancement of cocaine effects (the classic inverted U dose–response function). Individuals might titrate cocaine use over the course of a laboratory session so that they do not exceed an overall stimulant effect, leading them to choose fewer of the highest dose options while maintained on memantine.

Memantine maintenance was associated with an increase in diastolic pressure following cocaine. This effect was not observed in non-methadone-maintained volunteers (Collins et al., 1998), and it would seem to be an independent effect of memantine in the methadone-maintained population. Note that the memantine levels obtained in the current study are consistent with the range of levels previously reported in non-opioid-dependent individuals (Kornhuber and Quack, 1995) as well as the range of levels obtained during the induction and taper phases in a previous study from this laboratory (Collins et al., 1998). Thus, methadone maintenance does not appear to alter memantine plasma levels.

There was no effect of memantine maintenance on established tolerance to methadone, as measured by subjective ratings of opioid effects. Subjective and objective opioid withdrawal symptoms were also unaffected by memantine maintenance. Therefore, the current study suggests that individuals maintained on methadone may take moderate doses of low-potency NMDA antagonists for several weeks without significant risk of reduced tolerance and consequent opioid overdose from methadone.

There are a number of important issues to consider in the interpretation of the present findings. This study utilized a single dose of memantine (20 mg) given for a relatively brief period; therapeutic effects could occur with other doses of memantine or following longer maintenance periods. While the design of the current study allowed a direct comparison with earlier work, a drawback in the design allowing for this comparison was the utilization of a memantine dose previously found to be ineffective in reducing cocaine self-administration in a different population. The possibility of significant interactions between methadone and memantine argued for the conservative design using the same moderate memantine dosage; future studies in humans with a range of doses/maintenance schedules of memantine can now be carried out with fewer concerns about these interactions.

Other potential limitations in generalizing from this work should also be noted. First, in assessing potential interactions between methadone and memantine, the current study offers somewhat limited information. Although illicit opioid use among these patients prior to study inclusion was quite low, there was no quantitative measure of illicit opioid use during outpatient phases of the study. Such information would be illuminating about the potential for toxicities (including behavioral toxicities) associated with degree of heroin use in this setting. Another concern arises with the time course of methadone effects, as there can be significant fluctuations in methadone levels over the course of the day (Dyer et al., 1999; Hiltunen et al., 1995). These pharmacokinetic differences could produce significant changes in the effects of cocaine and/or memantine as a function of the time of day an individual is evaluated in the laboratory. In order to control for this possibility, the present study tested each dose of cocaine during memantine and placebo maintenance on one morning and one afternoon. Further, Foltin et al. (1995a) reported that the differences when cocaine was administered 1 h after methadone was administered versus 22 h after methadone was administered were subtle. Nevertheless, it is possible that important pharmacokinetic interactions between

methadone and memantine occurred; if so, the present study could not detect them. Compliance with the memantine administration was monitored indirectly by tracking the medication packaging and directly by weekly blood levels drawn during the outpatient periods. While the serum levels indicated that levels of memantine were present during the medication taper periods, it could be argued that a more suitable arrangement would have been to have research participants come to the laboratory every day for medication administration. However, we felt this would have placed an unwieldy burden on this sample and increased drop out rates for this study. Therefore we accepted that some medication might not be taken during the outpatient phases, but had 3 inpatient days before the study sessions began to monitor compliance.

In summary, the results of the present study suggest that memantine maintenance (20 mg/day) will not reduce cocaine self-administration or other cocaine effects in methadone-maintained cocaine smokers. Memantine maintenance in this population produces an increase in the effects of cocaine on diastolic pressure, but it does not appear to have any other interaction with methadone. Although the increases in diastolic pressure were statistically significant, they were not clinically significant. While there needs to be more attention to homogeneous sub-populations of cocaine abusers, particularly methadone-maintained cocaine abusers, it appears that memantine may not prove useful in this group. The possibility remains, however, that higher doses of memantine or other NMDA antagonists may yet prove helpful in the treatment of cocaine dependence.

Acknowledgments

This paper is dedicated to the memory of Marian W. Fischman, an inspired mentor to the authors. Her contribution to this work was significant, but she passed away prior to completion of this manuscript. This research was supported by Grants DA-10755 and DA-00317 from the National Institute on Drug Abuse. Research participants resided on the Irving Center for Clinical Research of the Columbia-Presbyterian Medical Center supported by Grant No. MOI-RR-00645 from the National Institutes of Health. The assistance of Dr. Daniel Bloomfield, Laura E. O'Brien, Lorraine Kemp, and Subuhee Hussain is gratefully acknowledged.

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