Effects of isradipine, a dihydropyridine-class calcium-channel antagonist, on d-methamphetamine’s subjective and reinforcing effects

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Abstract

In healthy human volunteers, we have previously shown that isradipine, a dihydropyridine-class calcium-channel antagonist, reduces some methamphetamine-induced positive subjective effects associated with its abuse liability, presumably by antagonizing cortico-mesolimbic dopamine pathways. In the present study, we combined acute immediate-release (IR) isradipine with repeated sustained-release (SR) isradipine pretreatment to determine whether isradipine could antagonize methamphetamine’s positive subjective and reinforcing effects in methamphetamine-dependent research subjects. We included 18 non-treatment-seeking, methamphetamine-dependent subjects aged between 18 and 51 years in this double-blind, within-subject, cross-over study, which was done in a human laboratory. Intravenous methamphetamine (0, 15 and 30 mg) was administered on three different days after 5 days of double-blind cross-over treatment with either isradipine or matching placebo. Subjects received oral isradipine 30 mg SR at bedtime, plus 15 mg IR administered 2 h before methamphetamine infusion. Self-report questionnaires measured drug liking, euphoria, craving, stimulation, and methamphetamine preference. Methamphetamine reinforcement was measured by a behavioural procedure involving choices between methamphetamine and money. For those who received isradipine second and placebo first as the pretreatment paradigm but not vice versa, methamphetamine-induced drug liking, elation, and preference were reduced significantly by isradipine. Depending upon conditioning status, isradipine can reduce some methamphetamine-induced positive subjective and reinforcing effects associated with its abuse liability in methamphetamine addicts.

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Introduction

Rates of methamphetamine abuse are rising again in the United States [Rawson et al., 2002; U.S. Department of Health and Human Services (DHHS), 1997]. In a survey of 21 U.S. metropolitan areas published by the Drug Abuse Warning Network, it was noted that methamphetamine-related emergency hospital attendances rose by 237% between 1990 and 1994, decreased 39% between 1994 and 1996, and increased 71% in the first 6 months of 1996 (U.S. DHHS, 1997). Given the high association between methamphetamine use, mental illness, violence, and HIV infection (Cho and Melega, 2002; Halkitis et al., 2001), it should come as no surprise that there has been great scientific and clinical interest in developing effective pharmacological agents to treat methamphetamine dependence (U.S. DHHS, 1997; Srisurapanont et al., 2001). Unfortunately, relatively few clinical trials have been conducted. Contemporary efficacy studies have examined the therapeutic potential of tricyclic antidepressants (e.g. imipramine) because of their ability to act either as substitution agents for mimicking...
similar pharmacological effects to those seen with chronic methamphetamine use – augmented catecholamine turnover rates and receptor down-regulation – or as preventive agents against negative affect (i.e. post-cessation symptoms of anxiety and depression) (Galloway et al., 1994, 1996). These studies failed to demonstrate efficacy for imipramine in the treatment of methamphetamine dependence.

A second therapeutic approach involves the use of medications that may reduce the rewarding and craving-related effects of methamphetamine (Hemby et al., 1997). Pre-clinical studies have implicated several midbrain neurotransmitters, especially dopamine (DA) and serotonin (5-HT), as being important mediators of the rewarding effects of amphetamine-like substances (Hemby et al., 1997). Testing medications that directly block the post-synaptic effects of central monoamines might not be a fruitful approach to identifying effective pharmacotherapy for stimulant addiction. One plausible explanation, although these mechanisms are not fully understood, is that central monoaminergic pathways exhibit high adaptability and compensatory mechanisms (Hemby et al., 1997), thus reversing any early treatment effects of direct antagonists to these neurotransmitter systems. Additionally, poor compliance with DA receptor blockers might limit their utility as practical treatments for psychostimulant use. In this respect, there is scientific and clinical interest in evaluating compounds that have functional effects of modulating these central midbrain systems (Hemby et al., 1997; Koob, 1992).

Amphetamines are psychostimulants whose reinforcing effects are primarily mediated by central midbrain monoamine pathways, particularly DA (Hemby et al., 1997; Koob, 1992; Wise et al., 1992). Amphetamines enhance DA neurotransmission primarily through DA release with modest inhibition of reuptake (Koob, 1992; Wise et al., 1992). d-Methamphetamine can produce neurotoxicity due to the destruction of DA and 5-HT axonal terminals and reduced vesicular monoamine transporter levels, and the extent of neuronal damage can be more widespread than that of d-amphetamine, which is more selectively associated with the destruction of DA axonal terminals (McCann and Ricaurte, 2004). d-Methamphetamine also differs from d-amphetamine in having a longer duration of action; however, their effects on monoamine release (Rothman et al., 2001) and their pharmacobehavioural profiles appear equipotent (Lamb and Henningfield, 1994). Notably, however, both DA release and uptake inhibition are calcium-channel-dependent processes (Mills et al., 1998). It is, therefore, of interest that the dihydropyridine-class calcium-channel antagonist, isradipine, has been shown to suppress both amphetamine-induced DA release (Pucilowski et al., 1995) and conditioned place preference (Calcagnetti and Schechter, 1992). Additionally, it has been hypothesized that other mechanisms of dihydropyridine-class calcium-channel antagonists contribute to their anti-reinforcing effects on amphetamines, such as interference with post-synaptic gene and hormone expression (Ernst et al., 2000; McCann et al., 1998; Volkow et al., 2000) and impulse propagation (Grace and Bunney, 1984; Overton and Clark, 1997). Thus, demonstrating that the dihydropyridine-class calcium-channel antagonists reduce the rewarding effects of amphetamines would provide additional support for the DA theory of brain reward.

In healthy human volunteers, we have shown that isradipine reduces some of the positive subjective effects of methamphetamine associated with its abuse liability (Johnson et al., 1999). Behavioural and neuroplasticity-related neuronal differences that can affect pharmacological response to isradipine can, however, exist between human volunteers and methamphetamine addicts. For instance, among healthy human volunteers, compared with methamphetamine addicts, methamphetamine-taking is a relatively novel event. Also, there is evidence that the long-term use of methamphetamine can be associated with neuronal damage to striatal and cortical DA and 5-HT axonal terminals and vesicular monoamine transporters (Ernst et al., 2000; McCann et al., 1998; Volkow et al., 1999) through auto-toxicity from elevated levels of DA’s enzymatic degradation product, 6-hydroxydopamine, and the increased release of glutamate (Eisch et al., 1996; Marshall et al., 1993). Thus, neuroplastic compensatory functional changes can be expected to lessen the capability of dopaminergic neurons in long-term methamphetamine-dependent individuals to respond to pharmacological agents (Davidson et al., 2001) that produce neuromodulation, such as dihydropyridine-class calcium-channel antagonists that exert their effects through calcium-dependent DA-mediated processes. Such an effect, although this was not tested directly, might explain why low doses of the dihydropyridine-class calcium-channel antagonist, amlodipine, in a preliminary 8-wk, placebo-controlled trial did not significantly reduce methamphetamine use or craving in methamphetamine-dependent individuals (Batki et al., 2001). In an attempt to prolong duration of action while maintaining relatively high peak levels of isradipine – to increase the likelihood of observing that isradipine
would diminish methamphetamine-induced increases in positive subjective and reinforcing effects—we optimized the isradipine dosing regimen by giving a combination of repeated doses of sustained-release (SR) isradipine plus a supplemental acute dose of the immediate-release (IR) preparation.

In summary, we tested the hypothesis that a combined repeated and acute isradipine dosing regimen would attenuate methamphetamine-induced positive subjective and reinforcing effects associated with its abuse liability in methamphetamine addicts.

Methods

Subjects

We studied 18 (14 males, 4 females) DSM-IV-diagnosed methamphetamine-dependent individuals. Subjects did not have any other major psychiatric disorders including schizophrenia, major depression, or bipolar disorder. Subjects were recruited by advertisement for methamphetamine-using individuals on the local radio and in newspapers, and all had histories of intravenous methamphetamine use for which they were not seeking treatment. In the month prior to study enrolment, subjects reported using methamphetamine and alcohol on a mean of 12.5 and 6.9 d respectively, and 16 subjects smoked a mean of 14.6 cigarettes/d. Subjects ranged in age from 18 to 51 yr (mean ± S.E. = 33.58 ± 2.42 yr) and weighed between 49.55 and 101.79 kg (mean ± S.E = 74.19 ± 13.77 kg). Fifteen of the 18 subjects were unemployed, and their ethnic distribution was White, 9; Hispanic, 4; Black, 2; and other, 3. All subjects gave informed consent prior to their inclusion in the study.

Design

This study was approved by the Institutional Review Board at The University of Texas Health Science Center at San Antonio and, therefore, was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. We conducted a double-blind, placebo-controlled, cross-over design that examined the effects of repeated doses of isradipine vs. placebo pretreatment on acute intravenous methamphetamine dose challenges. Subjects participated while residing on a locked hospital unit, the University Clinical Psychopharmacology Laboratory, located at the teaching hospital of The University of Texas Health Science Center at San Antonio. Each subject was admitted to the unit for two 8-d study periods separated by at least 1 wk. In one of these two study periods, subjects received oral doses of isradipine as a pretreatment, and in the other, they received placebo pretreatment, with the sequence (isradipine first or second) counter-balanced across subjects. Within each study period, all subjects received an open-label methamphetamine dose of 15 mg i.v. on the first day to ensure clinical tolerance to the methamphetamine dosing procedure for each individual subject. At 20:00 hours each evening, subjects received a double-blind oral dose of placebo (cornstarch) or isradipine SR (two tablets, each containing 15 mg plus cornstarch) contained within each of two opaque size 0 gelatin capsules. On days 4–7, subjects also received an oral dose of placebo or 15 mg isradipine IR at 11:00 hours. At 13:00 hours on days 5, 6 and 7, subjects received intravenous doses of placebo, 15 mg methamphetamine, and 30 mg methamphetamine respectively, administered under single-blind conditions. On day 8, subjects received either a monetary reward or one of the methamphetamine doses as selected by subjects on the Multiple-Choice Questionnaire (MCQ; described below).

Procedures

Each morning, subjects provided an alcohol-free breath sample and a urine specimen free from the presence of cocaine, opiates, amphetamines, benzodiazepines, and barbiturates as tested by OnTrak TesTcup® urine drug screen (Varian Inc., Palo Alto, CA, USA). Subjects received standard hospital meals three times per day. No caffeine-containing beverages were available at any time, and cigarette smokers were restricted to approx. 5–10 cigarettes/d, with none available for 1 h before or 1 h after intravenous dosing. All women of childbearing potential were placed on the oral contraceptive pill for the duration of the study as a method of contraception and to reduce menstrual cycle fluctuations in central DA function (Di Paolo, 1994; King et al., 1986).

Isradipine tablets were obtained from Sandoz Inc. (Vienna, Austria) and were over-encapsulated in opaque blue size 0 capsules and filled with cornstarch. Placebo isradipine capsules were identical in both colour and size and contained only cornstarch. Methamphetamine suitable for intravenous administration to humans was obtained from the National Institute on Drug Abuse. On days of intravenous dosing, subjects were seated in a comfortable lounge chair and instructed not to get up or talk for 15 min before and 60 min after dosing. One hour prior to insertion of the intravenous catheter, EMLA® Anesthetic Cream (AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) was applied topically to
minimize the discomfort of cannulation. The intravenous catheter was inserted into a non-dominant arm or hand vein and connected by polyethylene tubing to an automated syringe pump (Baxter International Inc., Deerfield, IL, USA). Subjects were monitored for safety by continuous electrocardiogram (Spacelabs Ultraview® 1050, Module 90496 cardiac monitor; Spacelabs Medical Inc., Issaquah, WA, USA), and heart rate and blood pressure were automatically recorded every 2 min for the entire period. A Baxter infusion pump was used to deliver a 2-ml volume of methamphetamine or placebo (saline) continuously over a 60-s period.

Subjects completed a visual analogue scale (VAS) to record subjective effects at 150 min and 30 min before methamphetamine or saline infusion, and after the infusion at eight 2-min intervals, three 15-min intervals, and four 30-min intervals, with the last measurement being 4 h post-infusion. Fourteen items were completed to record how the infusion made them feel: ‘right now’ on a 100-mm line anchored at the left and right extremes with ‘not at all’ and ‘extremely’ respectively. The individual items rated included: (1) measures of euphoria (‘high’, ‘like’, ‘rush or thrill’, ‘feel good or elated’); (2) measures of craving (‘crave’, ‘desire’, ‘want methamphetamine’, ‘could refuse methamphetamine’), and (3) general measures of stimulant effect/side-effect (‘aroused or stimulated’, ‘slow or lethargic’, ‘mind-racing’, ‘nervous’, ‘shaky or jittery’, and ‘nauseous’). At 6 h post-infusion, an End-of-Day Questionnaire asked subjects to express their overall (global) feelings about the effects of the methamphetamine dose they received earlier that same day (Roache and Meisch, 1995; Roache et al., 1995). For each of two statements, ‘I liked the overall effect of the methamphetamine dose’ and ‘I would use this methamphetamine dose again’, they were asked to record their responses on a 100-mm visual analogue line labelled from ‘not at all’ to ‘extremely’. Finally, subjects were asked to write down what they liked and what they disliked about the effect of the previous day’s methamphetamine dose.

At 150 min and 30 min pre-infusion, and at 30, 60, 120 and 180 min post-infusion, the Addiction Research Center Inventory (ARCI; Haertzen et al., 1963) was administered as a 49-item true/false questionnaire. Based upon empirically derived prototypical drug responses, the ARCI is subdivided into five factors called the MBG-euphoria, PCAG-sedation, A-amphetamine, BG-benzedrine, and LSD-dysphoria subscales. Also, at the same time-points, the Profile of Mood States (POMS; McNair et al., 1971) was administered as a 65-item questionnaire scored as eight factors including vigour, fatigue, friendliness, anger-hostility, tension-anxiety, depression-dejection, confusion-wilderment, and arousal. Additionally, the POMS-Elation (POMS-E) factor was administered as a 12-item bi-directional 5-point rating scale.

**Behavioural measure of reinforcement**

The MCQ was used to measure the reinforcing effects of the methamphetamine dose. It was a modification of the task originally developed by Griffiths et al. (1993). At 6 h post-infusion, subjects were asked to indicate their preference between receiving, at the end of the study phase, another dose of that day’s methamphetamine injection or, alternatively, various amounts of money. Across a series of 70 questions, the amount of the monetary alternative was sequentially increased in $0.25 increments from $0.25 to $10 and then in $0.50 increments from $10 to $25. The ‘cross-over value’ was assessed as the smallest amount of money that was preferred to methamphetamine. The cross-over value represents the approximate monetary value that subjects place upon the methamphetamine dose because preference for methamphetamine occurs at lower dollar amounts but money is preferred at this and greater amounts. During an initial training and familiarization session prior to the study, subjects were instructed that all of the choices they reported on the MCQ would be entered into a ‘lottery’ and that one of these choices would be randomly selected for them to receive the consequence of their choice selection. Of the 210 MCQ item questions (i.e. 70 items × 3 days) completed within each study phase, one was selected at random and used to determine what the subject would receive on the last day of each study phase. Thus, on day 8, subjects received either a methamphetamine dose or an amount of money as determined by their response on the randomly selected item. The actual receipt of an MCQ consequence makes this a reinforced response on a random probability schedule (Griffiths et al., 1996).

**Statistical analysis**

Data were analysed using Proc Mixed from Statistical Analysis System (SAS®) version 8.2 (SAS Institute Inc., 1999).

The experimental measures, such as the MCQ-Price, VAS, five-factor ARCI, and nine-factor POMS/POMS-E, were analysed with three-way analysis of variance in a mixed-effects model with first-order autoregressive (AR1) covariance structures, and using appropriate between- and within-error estimates.
methamphetamine measured at multiple time-points across each subject’s methamphetamine × isradipine dose combinations, and their dimensionalities were explored with area under the score-time curve (AUC) and peak scores. The AUC from 0 to 240 min was determined by the trapezoidal rule. Peak values were determined as maximal responses observed among the multiple post-infusion time measurements. MCQ-Price/Dose (between $0 and $25 of $40 available), End-of-Day drug liking, and the propensity to ‘use this methamphetamine dose again’ were only assessed at a single time-point. In these analyses, group (1, isradipine precedes placebo; or 2, placebo precedes isradipine), methamphetamine dose (0, 15 or 30 mg i.v.), and isradipine (1, present; or 0, absent) served as between-subjects effects, and the methamphetamine dose (0, 15 or 30 mg i.v.) and time (for the repeated measures) were the within-subject factors. We chose the auto-regressive covariance structure because it provided the best-fitting Akaike Information Criterion diagnostics among those we evaluated and was consistent also with the study design.

For all analyses, post-hoc Dunnett’s tests were performed only if there was a significant three-way interaction (group × isradipine × methamphetamine) or a two-way interaction (group × isradipine).

Results
For the VAS subscales, methamphetamine significantly increased (all p values < 0.05) all time-related AUC scores excluding the ability to ‘refuse’ methamphetamine. For ability to ‘refuse’ methamphetamine, there was a significant main effect of isradipine (p = 0.0009) (Table 1a); further, the contrast showed that those who received isradipine + methamphetamine 30 mg vs. placebo + methamphetamine 30 mg were more able to ‘refuse’ methamphetamine (p < 0.05). There was a significant interaction between isradipine × methamphetamine × group on ‘high’ (F = 4.77, p = 0.015), and in group 2, the isradipine + methamphetamine (15 mg) score was significantly lower than the placebo + methamphetamine score (p < 0.05). Methamphetamine significantly increased all peak effects scores excluding the minimum score on the ability to ‘refuse’ methamphetamine (all p values < 0.0001). For ability to ‘refuse’ methamphetamine, there was a significant main effect of isradipine (p = 0.02), indicating a generally enhanced ability to refuse, but none of the individual contrasts were significant (Table 1b). There was a significant interaction between isradipine × methamphetamine × group on ‘racing’ (F = 5.96, p = 0.006), and in group 1, the isradipine + methamphetamine (15 mg) score was significantly higher than the placebo + methamphetamine score (p < 0.01). There was no main effect of methamphetamine or isradipine on any of the other VAS subscales (data not shown).

For the ARCI subscales, methamphetamine significantly increased the BG-benzedrine (F = 6.11, p = 0.006), MBG-euphoria (F = 3.92, p = 0.03), and Amphetamine subscales (F = 5.49, p = 0.009) and decreased the PCAG-sedation (F = 5.94, p = 0.006) subscale. There was a significant interaction between isradipine × methamphetamine × group on BG-benzedrine (F = 3.25, p = 0.05) and PCAG-sedation (F = 4.88, p = 0.014) (Table 1a), and in group 2, the isradipine + methamphetamine (15 mg) score was significantly lower (i.e. less sedation) than the placebo + methamphetamine score (p < 0.05). There was no main effect of methamphetamine or isradipine on LSD-dysphoria (data not shown). Table 1b shows that methamphetamine significantly increased peak effects scores on all subscales except for PCAG, where there was a significant decrease. There was no main effect of isradipine or significant interaction between isradipine × methamphetamine × group.

For the POMS subscales, methamphetamine significantly increased AUC effects on vigour (F = 7.18, p = 0.003) and arousal (F = 7.81, p = 0.002), and decreased fatigue (F = 3.57, p = 0.04). There was no significant main effect of isradipine. There was a significant interaction between isradipine × methamphetamine × group on vigour (F = 5.72, p = 0.008) and arousal (F = 5.29, p = 0.01) (Table 1a); while there were no significant between-groups contrasts, there was a trend for the methamphetamine (15 mg) + isradipine scores to be lower than for methamphetamine (15 mg) + placebo. There was no main effect of methamphetamine or isradipine on any of the other POMS factors (data not shown).

Methamphetamine significantly increased peak effects on friendliness (F = 7.82, p = 0.002), vigour (F = 16.35, p < 0.0001), arousal (F = 16.66, p < 0.0001), and elation (F = 5.19, p = 0.01), and decreased fatigue (F = 3.46, p = 0.04). There was no significant main effect of isradipine. There was a significant interaction between isradipine × methamphetamine × group on vigour (F = 4.89, p = 0.014) and arousal (F = 3.83, p = 0.037) (Table 1b). In group 2, for vigour and arousal, the isradipine + methamphetamine (15 mg) score was significantly lower (i.e. less vigour and arousal) than the placebo + methamphetamine (15 mg) score (p < 0.05). There was no main effect of methamphetamine or isradipine on any of the other POMS factors (data not shown).
Table 1(a). Area under the curve self-report assessments with effects of isradipine or an interaction between isradipine and methamphetamine in 18 non-treatment-seeking, methamphetamine-dependent individuals

<table>
<thead>
<tr>
<th>VAS AUC (mm min)</th>
<th>Placebo</th>
<th>Isradipine</th>
<th>ANOVA</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean (s.e.)</td>
<td>Mean (s.e.)</td>
<td>Mean (s.e.)</td>
</tr>
<tr>
<td></td>
<td>Meth</td>
<td>0</td>
<td>15</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High 1</td>
<td>12.00</td>
<td>936.00</td>
<td>1227.00</td>
</tr>
<tr>
<td></td>
<td>(6.63)</td>
<td>(571.64)</td>
<td>(605.57)</td>
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<tr>
<td></td>
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<td></td>
<td>(17.42)</td>
<td>(159.83)</td>
<td>(302.33)</td>
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<td></td>
<td>(21.66)</td>
<td>(671.53)</td>
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<td>2</td>
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<td></td>
<td>(872.80)</td>
<td>(643.04)</td>
<td>(622.61)</td>
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<td>2</td>
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<tr>
<td></td>
<td>(654.91)</td>
<td>(667.66)</td>
<td>(853.02)</td>
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</table>

ARCI AUC (score min)

| PCAG 1 | 204.00 | 171.00 | 201.00 | 273.00 | 210.00 | 153.00 | 0.56 | 0.47 | 5.94 | 0.0064 | 4.88 | 0.014 |
|        | (60.63) | (24.92) | (54.05) | (65.03) | (67.23) | (33.30) |
|        | 2     | 296.25 | 258.75 | 153.75 | 236.25 | 161.25 | 191.25 |
|        | (55.96) | (48.75) | (21.54) | (19.17) | (17.87) | (32.54) |

POMS AUC (score min)

| Fatigue 1 | 51.00 | 39.00 | 78.00 | 234.00 | 78.00 | 90.00 | 0.35 | 0.56 | 3.57 | 0.0398 | 2.54 | 0.095 |
|          | (51.00) | (28.30) | (40.79) | (125.92) | (53.52) | (68.99) |
|          | 2     | 135.00 | 45.00 | 37.50 | 37.50 | 0.00 | 41.25 |
|          | (87.83) | (24.05) | (20.24) | (25.20) | (0.00) | (14.93) |
| Vigour 1 | 615.00 | 585.00 | 612.00 | 417.00 | 684.00 | 750.00 | 0.05 | 0.83 | 7.18 | 0.0027 | 5.72 | 0.008 |
|          | (129.09) | (136.62) | (134.77) | (90.93) | (102.55) | (155.43) |
|          | 2     | 532.50 | 806.25 | 735.00 | 596.25 | 667.50 | 843.75 |
|          | (175.55) | (156.03) | (180.62) | (156.14) | (185.00) | (150.58) |
| Arousal 1 | 564.00 | 519.00 | 516.00 | 192.00 | 600.00 | 690.00 | 0.06 | 0.81 | 7.81 | 0.0017 | 5.29 | 0.010 |
|          | (131.29) | (150.60) | (141.69) | (188.05) | (157.92) | (164.13) |
|          | 2     | 367.50 | 723.75 | 645.00 | 476.25 | 585.00 | 697.50 |
|          | (226.62) | (185.14) | (163.34) | (152.60) | (185.37) | (134.49) |

a (p < 0.008), b (p < 0.05), c (p < 0.055) represent significant mean differences between isradipine and placebo within each group and methamphetamine dose level.

Meth, methamphetamine; Isr, isradipine; s.e., standard error; ANOVA, analysis of variance; VAS, visual analogue scale; AUC, area under the curve; ARCI, Addiction Research Center Inventory; BG, benzedrine; PCAG, pentobarbital, chlorpromazine, and alcohol; POMS, Profile of Mood States.

In group 1 isradipine preceded placebo; in group 2 placebo preceded isradipine.
For MCQ-Price and End-of-Day Questionnaire ‘like effect’, there were significant main effects of methamphetamine ($F = 9.69$, $p = 0.0005$; and $F = 13.02$, $p < 0.0001$ respectively). Interestingly, there were trends for isradipine to decrease the likelihood to ‘use again’ ($p = 0.09$) and to ‘like effect’ ($p = 0.14$), and the isradipine × methamphetamine × group interaction was significant ($F = 3.95$, $p = 0.03$) on ‘like effect’. Isradipine vs. placebo treatment significantly reduced the ‘liking’ of methamphetamine in group 2, which achieved significance for at least the 15-mg methamphetamine dose (Figure 1).

Isradipine treatment was associated with two clinically significant adverse events. Fifteen of the 18 participants (83.3%) reported a total of 39 headache episodes during isradipine treatment, while only six participants (33.3%) reported a total of 12 headaches during placebo treatment. Headaches were typically mild to moderate in severity, mostly in the afternoons, and resolved either spontaneously or shortly after the administration of acetaminophen. Isradipine-related headaches began during the first few days of the isradipine pretreatment period for 13 subjects (i.e. 72.2%) but during the 3 d of the intravenous injection period,
the frequencies of headache reported were 19.6, 11.8 and 17.6% on the days of administration of the 0-, 15- and 30-mg methamphetamine doses respectively. Isradipine treatment was also associated with an increased frequency of palpitations \((7/18 = 38.9\%)\) reported a total of 12 incidents) relative to placebo treatment \((1/18 = 5.6\%\) reported one incident). These were not methamphetamine dose-related heart-rate increases since they occurred primarily on days on which methamphetamine was not administered.

Discussion
Overall, d-methamphetamine produced orderly increases in positive subjective and reinforcing effects associated with its abuse liability in these methamphetamine-dependent individuals. Interestingly, while the stimulant and reinforcing effects of methamphetamine generally were dose-related, the increases from 15 to 30 mg were fairly small compared with those between placebo and 15 mg methamphetamine. Indeed, we observed a similar effect of oral methamphetamine administration in healthy human volunteers (Johnson et al., 1999). In that study, we attributed this finding to ‘over-stimulation’ in naive subjects and cautioned that this possibility could not be established firmly as we did not have a methamphetamine-addicted group undergoing the same procedures with which to compare results. While extrapolation between studies must be undertaken with caution, it would appear that the similar finding of weak dose-dependency between 15 and 30 mg of methamphetamine might be more related to the fact that its stimulating effects build up relatively slowly, irrespective of dose, with a less defined peak, thereby diminishing the acuity with which subjects can distinguish clearly between doses within the narrow range tested herein.

Intriguingly, isradipine pretreatment attenuated only some of methamphetamine’s positive subjective...
(e.g. arousal and vigour) and reinforcing (i.e. less ‘like effect’ and increased ability to ‘refuse’) effects when it was given in the second experimental phase. That is, these subjects would have experienced the effects of methamphetamine doses alone (i.e. following placebo pretreatment) in the first phase of the study and then the methamphetamine + isradipine in the second phase. We think that there are at least five possible explanations for this finding.

First, individuals who got placebo as their initial pretreatment condition might have become conditioned to the maximal behavioural effects of unadulterated methamphetamine, thereby making it easier to discriminate between that condition and the less profound interactive effects when combined with isradipine. In other words, it may have been easier for these individuals during the second phase to perceive that this experience was not as clearly stimulating as the previous one.

Second, isradipine treatment was associated with normal adverse events, notably headaches. Therefore, the blinding of the study might have been unmasked in those who received isradipine pretreatment in the second phase, and this could have biased their assessments.

Third, it is possible that the non-central effects of taking isradipine and methamphetamine may have themselves interacted to produce cognitive dissonance in the subjects. For instance, both medications can produce tachycardia, albeit due to different mechanisms. Therefore, symptoms such as ‘racing’, which appear to be enhanced by the combination of isradipine and methamphetamine, may be due to a cognitive reinterpretation of peripheral effects. Paradoxically, this would lead to the conclusion that the optimal dose for isradipine to antagonize methamphetamine’s subjective and reinforcing effects might actually be lower than that tested, and that the actual balance to be struck is the administration of an isradipine dose that is sufficiently anti-reinforcing yet small enough to produce minimal peripheral symptoms, which could be misinterpreted as cognitive stimulant effects such as tachycardia. This rather counterintuitive consideration is strengthened by our previous observation, where we used a relatively lower isradipine dose to antagonize a comparatively higher methamphetamine dose (Johnson et al., 1999); however, important experimental differences preclude a direct comparison between that study and the present experiment.

Fourth, it also could be that a higher isradipine dose than that tested may be necessary to antagonize the positive and reinforcing effects of methamphetamine (15–30 mg) in methamphetamine addicts compared with healthy volunteers because of increased neuroplasticity and, therefore, less potential for neuro-modulation, or that interactions with other neuronal systems such as GABA (Dawirs et al., 1997) might be more important in this state. Nevertheless, even though we utilized the isradipine SR formulation to minimize the potential for cardiac-related adverse events, higher doses might be prohibitive and poorly tolerated and, therefore, counter-productive due to the emergence of other important adverse events such as headaches and palpitations.

Fifth, it is tempting to speculate that isradipine might have anti-reinforcing effects, even when administered alone. Isradipine’s anti-reinforcing effects might, therefore, have been masked in those who received it in the first phase because the novelty of receiving an illicit drug in a hospital environment might have overwhelmed this experience. This would imply that isradipine’s effects, using the present dosing regimen, on positive subjective and reinforcing effects are subtle and would only be more manifest in a study with greater statistical power to detect differences between treatment groups.

In summary, we found some evidence that isradipine can reduce some of methamphetamine’s positive subjective and reinforcing effects under certain conditions. The dependence of this effect on previous methamphetamine dosing in the absence of isradipine (i.e. group 2, who received placebo treatment first) is not necessarily a discouraging finding. While it may be unique to the experimental setting, it also may indicate that isradipine works best in methamphetamine-habituated environments, which would often be the case in the natural environments encountered by outpatients in their natural setting. Further studies are needed to elucidate the reasons for isradipine’s partial anti-reinforcing effects in methamphetamine addicts to determine whether it might have some utility as a putative therapeutic agent.

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Statement of Interest
None.

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