Effects of isradipine on cocaine-induced changes in cognitive performance in recently abstinent cocaine-dependent individuals

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Abstract

Recently abstinent cocaine-dependent individuals, compared with healthy controls, appear more likely to exhibit deficits in cognitive performance and attention. Individuals with such cognitive deficits might be less able to avail themselves of rehabilitative or relapse-prevention efforts. Pharmacotherapy that reduces the impairment in cognitive performance among cocaine-dependent individuals would be a useful clinical tool. Preclinical and human studies suggest that the dihydropyridine-class calcium-channel antagonist, isradipine, can enhance neurocognitive function in some neuropsychiatric disorders. Isradipine, presumably by increasing cerebral blood flow and its actions at various neurotransmitter systems, might, therefore, ameliorate the impairment in cognitive performance and attention seen in cocaine addicts and enhance the expected modest improvement in performance during acute cocaine-taking in these same individuals. Among 12 male and female cocaine-dependent individuals, we examined the effects of low and high doses of intravenous cocaine (0, 0.325, and 0.650 mg/kg) on cognitive performance and attention in both the presence and absence of isradipine (0 or 30 mg sustained release each evening prior to testing, plus 0 or 15 mg immediate release each morning 2 h before the cocaine or placebo cocaine infusion and on the day of testing). Intravenous cocaine produced a modest increase in cognitive performance and attention. Isradipine, both with and without cocaine, had no effect on these same parameters. Hence, cocaine-taking by cocaine-dependent individuals produces little improvement in cognitive performance and attention in either the presence or absence of isradipine.

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Introduction

Despite the growing number of human pharmaco-behavioural studies that have been conducted on the effects of cocaine, there remains relatively little information on the effects of intravenous cocaine administration on cognitive performance in recently abstinent cocaine-dependent individuals.

A series of controlled studies have shown that the pattern of neuropsychological deficit among chronic cocaine users, compared with healthy age- or age- and education-matched controls, depends upon the length of use (Ardila et al., 1991; Rosselli and Ardila, 1996), whether there is current drug-taking (Berry et al., 1993) or significant poly-drug use (Rosselli and Ardila, 1996), and the period of time between the abstinence period and when testing was conducted (Manschreck et al., 1990; Strickland et al., 1993). Typically, chronic cocaine use has been associated with impairments in sustained attention and concentration (Ardila et al., 1991; Beatty et al., 1995; Di Scalfani et al., 2002), memory (O’Malley et al., 1992; Rosselli and Ardila, 1996; van Gorp et al., 1999), spatial reasoning (Holman et al., 1991), spatial relations (Robinson et al., 1999), manual dexterity, and psychomotor performance (Bolla et al., 2000; Herning et al., 1990; Roberts and
Bauer, 1993; Robinson et al., 1999). Importantly, there have, however, been some contradictory findings as well as difficulties comparing results across studies because of variations in defining an adequate sample size, inappropriate controls, inconsistent timing, and choice of the neuropsychometric assessment battery (Lawton-Craddock et al., 2003). The importance of these findings is that neurocognitive deficits in recently abstinent cocaine-dependent individuals increase the chances of relapse into drug-taking because such individuals will have reduced capacity to make full use of rehabilitation facilities (Gillen et al., 1998). Further, the desire to prevent cognitive deterioration following acute abstinence, and, therefore, decreased psychosocial functioning, may itself be a trigger that maintains cocaine-taking. This cocaine-taking-associated maintenance or protection of neurocognitive impairment might be more related to increased levels of general arousal due to enhanced catecholaminergic function, and would be expected to be relatively short-lived and follow the time-course of drug administration. Hence, a pharmacological adjunct that could prevent cognitive deterioration during abstinence could be a useful tool towards aiding rehabilitative efforts among cocaine-dependent individuals.

Isradipine is a dihydropyridine-class calcium-channel antagonist that has been shown to improve learning and performance in animals (Quevedo et al., 1998). In humans, there is clinical evidence that dihydropyridine-class calcium-channel antagonists may improve age-associated and Alzheimer-related memory impairment (Heidrich et al., 1997; Yamada et al., 1996) in addition to improving learning and memory in schizophrenic patients (Schwartz et al., 1997). Thus, dihydropyridine-class calcium-channel antagonists can enhance cognition in some neuropsychiatric conditions (Vetulani et al., 1997). Further, it has been proposed (Bauer, 1993, 1994) that the cocaine-associated impairment in perceptual-motor speed, reaction time, and tests of attention may be consistent with the pattern of reductions in cerebral blood flow, particularly in the frontal and temporoparietal cortices, among cocaine-dependent individuals recorded by positron emission tomography (Volkow et al., 1988), single photon emission computerized tomography (Johnson et al., 1998a), and magnetic resonance imaging (Strickland et al., 1993). Hence, chronic cocaine use can be associated with impairment on tests of performance and cognitive processing, particularly those associated with decision-making, due to dysfunction of the orbitofrontal cortex (Goldstein and Volkow, 2002). Since isradipine has been shown to attenuate cocaine-associated reductions in cerebral blood flow (Gottschalk and Kosten, 2002; Johnson et al., 1998b, 2001), presumably by antagonizing cocaine-associated increases in central dopamine function (for a review, see Johnson et al., 2001), isradipine may have utility in reducing impairments in perceptual-motor speed, reaction time, and attention among cocaine-dependent individuals.

In the present study, we tested the hypothesis that intravenously administered cocaine would be associated with time- and dose-dependent increases in the neurocognitive tasks of perceptual-motor speed, reaction time, and attention, and that isradipine would enhance these cocaine-taking-associated improvements on the same tasks.

Materials and methods

Subjects

We studied 12 individuals (11 males, 1 female) with histories of intravenous drug use who met DSM-IV criteria (APA, 1994) for cocaine dependence. We did not enrol subjects who met diagnostic criteria for Axis I psychiatric disorder or any other substance dependence besides nicotine dependence. Subjects were mostly black, with a mean age of 38.5 yr, and none were presently married (58.3% had never married) (Table 1). All subjects were recruited from the community by advertisement in the local radio and newspaper media for stimulant-using research volunteers who were not seeking treatment. Additionally, subjects provided written informed consent approving their participation in the study. All subjects were hospitalized during the entire study at the University Clinical Psychopharmacology Laboratory, a residential research unit at the University Hospital, the main teaching hospital of The University of Texas Health Science Center at San Antonio.

Experimental design

This study was approved by the Institutional Review Board at The University of Texas Health Science Center at San Antonio and was, therefore, performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The experiment was a double-blind, placebo-controlled, cross-over design that examined the effects of repeated doses of isradipine vs. placebo pretreatment on intravenous cocaine dose challenges. 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) counterbalanced across subjects. Within each study period, all subjects received an open-label cocaine dose (0.325 mg/kg) intravenously on the first day to ensure clinical tolerance to the cocaine dosing procedure for each individual subject. At 20:00 hours each evening, subjects received an oral dose of placebo (cornstarch) or isradipine (two whole tablets of 15 mg sustained release 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 (immediate release) at 11:00 hours. At 13:00 hours on days 5, 6, and 7, subjects received intravenous doses of placebo, 0.325 mg/kg cocaine, and 0.650 mg/kg cocaine respectively, administered under single-blind conditions. General 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 ~5–10 cigarettes/d, with none available for 1 h before or 1 h after intravenous dosing. The female subject was placed on the oral contraceptive pill for the duration of the study as a method of contraception and to reduce natural menstrual cycle fluctuations in central dopamine function (Di Paolo, 1994; King et al., 1986).

Isradipine tablets obtained from Sandoz Inc. (Vienna, Austria) 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. Cocaine 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 remained there from 15 min before until 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), which delivered a 2-ml volume of cocaine or placebo (saline) continuously over a 60-s period. Subjects were monitored for safety by continuous electrocardiogram and frequent heart rate and blood pressure recordings with the Spacelabs Ultraview® cardiac monitor (Spacelabs Medical Inc., Issaquah, WA, USA). During the experiment, measures of cognitive performance were done 30 min prior to dosing and at 30, 60, and 120 min post-dosing. Behavioural measures of euphoria, craving, and drug reinforcement also were collected at scheduled intervals; these findings have been described elsewhere (Johnson et al., 2004; Roache et al., In Press).

Measures of cognitive performance

We evaluated cognitive performance using two standardized and well-validated methods.

Rapid visual information processing task

The rapid visual information processing task (RVIPT) is a recognized test of attention and concentration (Johnson et al., 1996; Silverstone et al., 1992). In the RVIPT, subjects monitor digits that are presented...
sequentially on a computer screen at a rate of 100/min for 7.5 min. Subjects are instructed to detect and respond to targets of three consecutive even or odd digits as quickly as possible. Independent measures are made of both the speed and the accuracy of decision-making. These measurements are recorded for each trial block: hits – correct responses within 600 ms; delayed hits – responses that occur between 600 ms and 1200 ms after the target; false alarms – incorrect responses, and reaction time for both hits and delayed responses.

**Digit symbol substitution test**

The digit symbol substitution test (DSST) has been used frequently to measure sedative impairment of perceptual-motor function. A computerized version of the task (McLeod et al., 1982) has demonstrated dose-related impairment with ethanol (Mintzer et al., 1997; Roache et al., 1993). The task requires subjects to depress key positions on a numeric keypad to reproduce geometric symbol patterns displayed on the computer screen. The data are the number of patterns correctly reproduced out of the number attempted during a 90-s test session. Although this is an integrative task involving perceptual and motor components, its measures of both speed and accuracy are sensitive to the effects of drugs that can produce either psychomotor acceleration or retardation.

**Statistical analysis**

The cognitive performance measures, RVIPT and DSST, were assessed at multiple time-points for each subject’s cocaine × isradipine dose combination, and their dimensionalities were explored with peak and area under the curve (AUC) effects. AUC measurements were obtained by using the trapezoidal rule and were normalized to the hour along the x-axis. The cocaine peak effects were determined by examinations of maximal responses for all variables except for reaction time, for which we determined the minimum among the multiple measurements of post-cocaine infusion.

The RVIPT – which includes four categories: number of hits, number of delayed hits, number of false alarms, and reaction time – and the DSST – which includes two categories: total responses and total correct responses – were analysed with two-way analysis of variance (ANOVA) in mixed-effects models with first-order autoregressive covariance structures. Log-transformations were performed as needed to meet the normality criteria.

All data were analysed with univariate ANOVA using Proc Mixed from the Statistical Analysis System® Version 8.2 (SAS Institute Inc., 1999). The ANOVA model was a repeated-measures 2 × 3 factorial including isradipine dose level (0 and 1) and cocaine dose level (placebo, low, and high doses) plus their interactions with four levels of time for RVIPT and DSST recordings. To examine maximal cocaine effects, ‘peak’ effect values were determined for each subject as the maximal observation occurring during the post-cocaine infusion time-course. In these analyses, cocaine dose [0 = placebo, 1 = low-dose cocaine (0.325 mg/kg i.v.), or 2 = high-dose cocaine (0.650 mg/kg i.v.)] and isradipine (1 = present or 0 = absent) served as between-subject effects, and the cocaine day (1, 2, or 3) nested in the isradipine day (1 or 2) served as the within-subject factor. We planned to use post-hoc Dunnett’s tests to compare isradipine with placebo within the cocaine dose-level effects if there was a significant interaction on the ANOVA.

**Results**

On peak RVIPT response, there was a main effect of cocaine to increase the total log number of hits (p = 0.02) and reduce the number (log) of false alarms (p = 0.03). There was no main effect of isradipine and no interaction between isradipine and cocaine on peak RVIPT response. For peak DSST response, there was a main effect of cocaine to increase the total number of responses (p = 0.02) but not the total number of correct responses. There was no main effect of isradipine and no interaction between isradipine and cocaine on peak DSST response (Table 2a).

On AUC RVIPT response, there was a main effect of cocaine to increase the total log number of hits (p = 0.007). There was no main effect of isradipine and no interaction between isradipine and cocaine on AUC RVIPT response. For AUC DSST response, there was a main effect of cocaine to increase the total number of responses (p = 0.008) and the total number of correct responses (p = 0.04). On the AUC DSST measure, there was no main effect of isradipine and no interaction between isradipine and cocaine (Table 2b).

**Discussion**

Intravenous cocaine administration was associated with a small improvement in psychomotor performance and attention, but these were not dose dependent; indeed, there was a non-significant trend for the lower cocaine dose to be associated with greater improvement. Peak response occurred at 60 min.
### Table 2(a). Peak effects of isradipine on cognitive assessments of 12 non-treatment-seeking, cocaine-dependent individuals

<table>
<thead>
<tr>
<th>Measure of cognitive performance</th>
<th>Placebo</th>
<th>Isradipine</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.E.)</td>
<td>Mean (S.E.)</td>
<td>Mean (S.E.)</td>
</tr>
<tr>
<td>Coc dose (mg/kg, i.v.) ...</td>
<td>0</td>
<td>0.325</td>
<td>0.650</td>
</tr>
<tr>
<td>Log-total hits (counts)</td>
<td>3.54 (0.11)</td>
<td>3.66 (0.09)</td>
<td>3.61 (0.10)</td>
</tr>
<tr>
<td>Log-delayed hits (counts)</td>
<td>1.95 (0.17)</td>
<td>1.92 (0.19)</td>
<td>2.03 (0.17)</td>
</tr>
<tr>
<td>Log-false alarms (counts)</td>
<td>2.38 (0.34)</td>
<td>2.26 (0.33)</td>
<td>2.35 (0.28)</td>
</tr>
<tr>
<td>Reaction time (ms)</td>
<td>446.17 (20.28)</td>
<td>466.61 (18.20)</td>
<td>464.00 (15.73)</td>
</tr>
<tr>
<td>RVIPT</td>
<td>46.25 (2.54)</td>
<td>48.33 (2.43)</td>
<td>48.09 (2.45)</td>
</tr>
<tr>
<td>DSST</td>
<td>44.58 (2.77)</td>
<td>46.17 (2.28)</td>
<td>46.01 (2.23)</td>
</tr>
</tbody>
</table>

Coc, Cocaine; Isr, isradipine; ANOVA, analysis of variance; RVIPT, rapid visual information processing task; DSST, digit symbol substitution test.

### Table 2(b). AUC effects of isradipine on cognitive assessments of 12 non-treatment-seeking, cocaine-dependent individuals

<table>
<thead>
<tr>
<th>Measure of cognitive performance</th>
<th>Placebo</th>
<th>Isradipine</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.E.)</td>
<td>Mean (S.E.)</td>
<td>Mean (S.E.)</td>
</tr>
<tr>
<td>Coc dose (mg/kg, i.v.) ...</td>
<td>0</td>
<td>0.325</td>
<td>0.650</td>
</tr>
<tr>
<td>RVIPT AUC</td>
<td>7.71 (0.12)</td>
<td>7.83 (0.10)</td>
<td>7.79 (0.09)</td>
</tr>
<tr>
<td>Log-total hits (counts × min)</td>
<td>5.79 (0.18)</td>
<td>5.65 (0.24)</td>
<td>5.78 (0.23)</td>
</tr>
<tr>
<td>Log-delayed hits (counts × min)</td>
<td>6.01 (0.44)</td>
<td>6.05 (0.42)</td>
<td>6.16 (0.29)</td>
</tr>
<tr>
<td>Reaction time (ms × min)</td>
<td>36472 (1392)</td>
<td>36236 (1493)</td>
<td>36640 (1310)</td>
</tr>
<tr>
<td>DSST AUC</td>
<td>3322.50 (185.38)</td>
<td>3490.00 (181.17)</td>
<td>3436.81 (186.58)</td>
</tr>
</tbody>
</table>

AUC, Area under the curve; Coc, cocaine; Isr, isradipine; ANOVA, analysis of variance; RVIPT, rapid visual information processing task; DSST, digit symbol substitution test.
post-cocaine infusion, and these effects tailed off thereafter (data not shown). There was no effect of isradipine, either alone or in combination with cocaine, to improve psychomotor performance or attention.

One striking facet of these results is that acute intravenous cocaine administration produces only modest enhancement of psychomotor performance and attention. This effect has been attributed to the masking of cocaine’s cognition-enhancing potential by the cognition-impairing effects of the rapid rise in cortisol caused by administering cocaine acutely via the intravenous route (for a discussion, see Hopper et al., 2004).

Since chronic cocaine users compared with healthy controls possess cognitive deficits, and there is a positive correlation between the level of cognitive functioning and treatment success with teaching coping skills to maintain recovery (Aharonovich et al., 2003), rehabilitative efforts that include a medication that is efficacious at improving cognition would be an important therapeutic adjunct.

Unfortunately, however, our study results do not support an important role for isradipine as an aid to improving neurocognitive function and performance among cocaine-dependent individuals. There are at least five plausible reasons for this lack of effect. First, isradipine might have to be administered chronically to restore cocaine-associated perfusion deficit fully and enable neuronal recovery. Second, cocaine-associated impairment in neurocognitive function may not simply be the result of acute cerebral hypoperfusion but may actually be more the consequence of prolonged ischaemia, and consequently neuronal death, which cannot be reversed by isradipine treatment. Third, dihydropyridine-class calcium-channel antagonists have been shown to reduce memory-related impairments in individuals with Alzheimer’s disease (Birkenhager et al., 2000). These cognition-enhancing effects appear to be modulated by non-catecholaminergic mechanisms and, in particular, by increased acetylcholine activity. Nevertheless, individuals with Alzheimer’s disease do not appear to experience increased attention following the administration of a dihydropyridine-class calcium-channel antagonist (Besson et al., 1988). Therefore, dihydropyridine-class calcium-channel antagonists might influence cognitive processes other than performance and attention. Further support for this impression comes from our own finding in non-fatigued healthy human volunteers that isradipine treatment has no significant effect on attention (Johnson et al., 2000). Fourth, while we, of course, considered the possibility that our inability to demonstrate clearer effects could be due to the relatively small sample size in our study, an inspection of group means and their standard errors would suggest that if the effect size between the active treatment and placebo conditions remained unchanged, even a cohort many times larger would not yield a different result. Fifth, although we speculated about whether the administration of a higher isradipine dose than that used in the present study would have resulted in increased attention or perceptual-motor function, such a premise would be difficult to test empirically, and would not be of practical therapeutic importance, because of the considerable risk of serious adverse events with a higher isradipine dosing regimen.

In summary, we propose that intravenous cocaine is associated with a modest and transient increase in cognitive performance and attention; however, these effects did not vary by dose. Isradipine, either alone or in combination with cocaine, does not appear to have any important effects on psychomotor performance or attention among cocaine-dependent individuals.

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Statement of Interest

None.

References


