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The safety, tolerability and subject-rated effects of acute intranasal cocaine administration during aripiprazole maintenance II: Increased aripiprazole dose and maintenance period

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Abstract

Objectives—This experiment determined the safety and tolerability of intranasal cocaine during aripiprazole maintenance.

Methods—Six cocaine-dependent human subjects were maintained on aripiprazole (15 mg) and placebo for 10 days in counterbalanced order prior to assessing the physiological and subject-rated effects of intranasal cocaine.

Results—Intranasal cocaine produced prototypical stimulant-like effects (e.g., increased blood pressure and heart rate, increased subject ratings of Like Drug and Stimulated) and aripiprazole enhanced these effects on several measures.

Conclusions—15 mg/day aripiprazole is safe and tolerable when combined with cocaine; however, the usefulness of aripiprazole as a treatment for cocaine-use disorders remains to be determined.

Keywords

aripiprazole; cocaine; pharmacotherapy; subjective effects; physiological effects

INTRODUCTION

The illicit use of cocaine remains a significant public health concern, yet a widely effective pharmacotherapy for cocaine dependence has not been identified (1). Recently, the atypical antipsychotic aripiprazole (Abilify®) has been the focus of preclinical and clinical evaluations as a potential pharmacotherapy for stimulant use-disorders (2–5). The initial interest in aripiprazole stemmed from its unique mechanism of action as a partial agonist at dopamine D₂ dopamine receptors and dopamine system stabilizer (6). Partial agonists are effective for opiate and nicotine dependence and dopamine D₂ receptors have been implicated in the abuse-related effects of cocaine; therefore, aripiprazole might be an effective strategy for cocaine dependence (7). We previously examined the safety, tolerability and subject-rated effects of

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acutely administered intranasal cocaine in cocaine-dependent subjects maintained on 10 mg aripiprazole for seven days (3). Aripiprazole was generally devoid of effects, but did alter the hyperthermic and a subset of subject-rated effects of cocaine as a function of dose. The purpose of the present experiment was to determine the safety, tolerability and subject-rated effects of acute cocaine during maintenance on a higher dose of aripiprazole (15 mg) administered for ten days.

METHOD

Subjects

Six subjects (5 males, 1 female; 5 African American, 1 Caucasian), who met criteria for cocaine dependence, but not for any other current psychiatric diagnosis, as determined by a computerized version of the Structured Clinical Interview for the DSM-IV, completed this placebo-controlled experiment. Subjects all reported current crack cocaine use (257 ± 84 mg in the week prior to enrollment), which was verified via cocaine-positive urine test results. All subjects completed comprehensive medical and psychological screens and were without contraindication to the drugs administered in the protocol. Six additional subjects were enrolled but did not complete the protocol.

Procedures

Subjects were enrolled as inpatients at the University of Kentucky Chandler Medical Center General Clinical Research Center (GCRC) for up to 24 days. Subjects were maintained on a caffeine-free diet and participated in one practice and two experimental sessions. Urine and expired breath samples were collected at the outset of every session to confirm drug and alcohol abstinence. The female subject was also screened for pregnancy prior to each session.

The Medical Institutional Review Board of the University of Kentucky approved this study, and all subjects gave sober, written informed consent. Subjects were paid for their participation.

Practice Sessions—Subjects completed one “practice” session to familiarize them with the daily laboratory routine and experimental measures, but did not receive drugs.

Drug Maintenance Days—Drug maintenance began on the day immediately following the practice session and continued throughout the protocol. Placebo or 15 mg aripiprazole was administered orally at 2200 (h). After maintenance on the starting condition, subjects completed the first experimental session (described below), and subsequently were switched to the other maintenance condition after which they then completed a second experimental session. The order of the maintenance conditions was counterbalanced. The duration of each maintenance period was 10 days, with the following exceptions. Due to a nursing staff error, two subjects received 15 mg aripiprazole for 11 days and one subject received it for 9 days.

Experimental Sessions—Experimental sessions started at 0800 h and lasted 6.5 h. Four intranasal cocaine doses were given each session in ascending order 1.5 h apart [4, (placebo), 20, 40 and 80 mg]. Subjects completed all experimental measures prior to drug administration and at 15 min intervals for one hour after each cocaine dose. Subsequent doses of intranasal cocaine were administered every 1.5 hours and experimental measures were completed on the same schedule. If heart rate exceeded 130 beats per minute, systolic blood pressure exceeded 180 mmHg, diastolic blood pressure exceeded 120 mmHg or clinically significant ECG changes occurred following administration of cocaine at any point during the experiment, participation was terminated. No subject was excluded from participation for exceeding these parameters.

Physiological and Subject-Rated Measures

Blood pressure, heart rate and temperature were recorded using a Dinamap Pro 1000 Vital Signs monitor (Critikon, Tampa, FL). Subject-rated measures included an Adjective Rating Scale (8), a modified version of a Cocaine Craving Questionnaire (9), a Stimulant Sensitive Adjectives Scale (10) and a locally developed Drug-Effect Questionnaire (11). In addition, a locally developed Visual Analog Scale Questionnaire was used that included the 10 items "Is the Drug Making You Feel: Active, Alert and Energetic; Euphoric; Talkative, Friendly; High, or Stimulated Right Now?", "Is the Drug Producing any Good Effects Right Now?", "Are You Experiencing a Rush from the Drug Right Now?", "How Much Do you Like the Drug Effects Right Now?", "Based on How the Drug Effect Feels Right Now, Would you be Willing to Take the Drug Again?" and "Based on How the Drug Effect Feels Right Now, Would you be Willing to Pay For this Drug?". GCRC nursing staff completed the Barnes Akathisia Scale, Abnormal Involuntary Movement Scale, the UKU Side Effects Scale and the Simpson Angus Scale with the subjects daily (13–16). Although not analyzed statistically, visual inspection of these scales by unit physicians revealed no clinically significant changes throughout study participation. Moreover, blood glucose levels were tested before and after study participation and were normal.

Drug Administration

All drugs were administered in a double-blind fashion. Aripiprazole (0 and 15 mg; Bristol-Myers Squibb, New York, NY) doses were prepared by encapsulating commercially available drug in a size-0 capsule with cornstarch. Placebo capsules contained only cornstarch.

Cocaine doses [4 mg (placebo), 20, 40 and 80 mg] were prepared by combining the appropriate amount of cocaine HCl (Mallinckrodt, St. Louis, MO) with lactose to equal a total of 100 mg powder. During each administration, a nurse presented the subject with the powder, a mirror and a standard razor blade. The subject was then instructed to divide the powder into two even "lines" and insufflate one line of powder through each nostril using a 65-mm plastic straw within 2 minutes.

Data Analysis

Data from the experimental sessions were analyzed as peak effect (i.e., the maximum score observed following each drug administration) using a two factor repeated-measures ANOVA with Aripiprazole (0 and 15 mg) and Cocaine [4 mg (placebo), 20, 40 and 80 mg] as the factors (JMP, SAS Institute, Cary, NC). F values from the ANOVA were used to interpret the results. Effects were considered significant for $p \leq 0.05$.

RESULTS

Cocaine dose-dependently increased Systolic Blood Pressure, Heart Rate and Temperature (i.e., significant main effects of Cocaine; $F_{3,15}$ values > 6.5 , p 's < 0.01 ; Figure 1). Aripiprazole alone increased Heart Rate and enhanced the increasing effects of cocaine (i.e., significant main effect of Aripiprazole; $F_{3,15} = 15.1$, $p = 0.01$; Figure 1).

Cocaine dose-dependently increased subject ratings on the Total Score on the Stimulant Sensitive Adjectives (i.e., significant main effect of Cocaine; $F_{3,15} = 3.3$, $p = 0.05$) and aripiprazole did not modulate these ratings (data not shown).

Cocaine increased subject ratings on five items from the Drug-Effect Questionnaire: Like Drug, Take Again, Willing to Pay For, Any Effect and Performance Impaired. For the items Like Drug, Take Again and Willing to Pay For, aripiprazole enhanced the effects of cocaine (i.e., significant interaction of Aripiprazole and Cocaine; $F_{3,15}$ values > 3.1 , p 's < 0.05) (Figure 1).

For the items Any Effect and Performance Impaired, aripiprazole did not significantly modulate the effects of cocaine (i.e., significant main effect of Cocaine; $F_{3,15}$ values > 4.0 , p 's ≤ 0.05 ; data not shown). Aripiprazole also increased subject ratings of Stimulated (i.e., significant main effect of Aripiprazole; $F_{1,5}$ value = 6.7, $p < 0.05$; data not shown).

Cocaine also increased subject ratings on three items from the Visual Analog Scale Questionnaire: Stimulated, High and Willing to Pay For. For the item Stimulated, aripiprazole enhanced the effects of cocaine (i.e., significant interaction of Aripiprazole and Cocaine; $F_{3,15} = 3.4$, $p < 0.05$; Figure 1). For the items High and Willing to Pay For, aripiprazole did not significantly modulate the effects of cocaine (i.e., significant main effect of Cocaine; $F_{3,15}$ values > 3.1 , p 's ≤ 0.05).

DISCUSSION

The results of the present experiment indicate that acute administration of cocaine is safe and tolerable during maintenance on a higher dose of aripiprazole. Intranasal cocaine produced prototypical stimulant-like effects (e.g., increased blood pressure and heart rate, increased subject ratings of Like Drug and Stimulated) and aripiprazole enhanced these effects on several measures.

In our previous study in which the subject-rated and cardiovascular effects of intranasal cocaine were tested during maintenance on 10 mg/day aripiprazole for seven days, aripiprazole was generally devoid of effects, although it did enhance the effects of the highest cocaine dose tested (60 mg) on a couple of the items from the self-report questionnaires (3). Consistent with that initial study, maintenance on 15 mg/day aripiprazole for ten days appeared to enhance many of the cardiovascular and subject-rated effects of intranasal cocaine in the present study, primarily at the highest cocaine dose (80 mg). Worth noting, however, is that the dose-effect function for cocaine was an inverted-U shape, instead of a monotonically increasing function of dose. An increase in the effects of a cocaine dose on the descending limb of the dose-effect function could be interpreted as antagonism of that dose. However, the effects of cocaine on heart rate, which increased with dose, were also enhanced by aripiprazole treatment. In addition, preliminary data from another laboratory suggest that 17 days of maintenance on 15 mg/day aripiprazole increased the reinforcing effects of 12 and 25 mg smoked cocaine (17). Taken together, it appears that aripiprazole maintenance enhances several of the effects of cocaine. The mechanism for this enhancement is not clear. A dopamine D_2 antagonist partial agonist would be expected to function as an antagonist under conditions of increased dopamine tone, such as in the presence of cocaine (18). One possibility is that maintenance on aripiprazole produced neuroadaptive changes in dopamine systems that enhanced or restored sensitivity to cocaine. Consistent with this hypothesis, a large body of literature has demonstrated increased sensitivity of dopamine systems following chronic D_2 antagonist administration. In one study, for example, treatment with haloperidol increased the locomotor response to cocaine in rats (19).

The results from the present study are in contrast, however, to the data from our previous studies in which 10 and 20 mg aripiprazole were tested in combination with a range of doses of *d*-amphetamine (2,20). In those studies, both drugs were administered on an acute basis, and aripiprazole attenuated the discriminative-stimulus, subject-rated and/or cardiovascular effects of *d*-amphetamine. Those data are in agreement with preclinical research demonstrating that acute aripiprazole decreases the reinforcing effects of methamphetamine (5) and the locomotor stimulating effects of *d*-amphetamine (21). The reasons for the discrepancies are unknown, but could be due to duration of treatment (i.e., sub-chronic versus acute), differences in the mechanism of action of cocaine versus the amphetamines or the subject population enrolled in the clinical studies (i.e., dependent versus non-dependent subjects).

Aripiprazole was well tolerated in all six subjects who completed the protocol. However, one subject experienced extrapyramidal symptoms during aripiprazole maintenance. Following the appropriate symptom management and medical follow-up, this subject was discharged from the protocol. This subject's data were not included in the analysis. This incident suggests that 15 mg/day aripiprazole might be approaching the upper limit of what would be useful in treating cocaine-dependent individuals. Given that 10 mg of aripiprazole appears to be the lower threshold of effective doses to alter the effects of stimulants such as cocaine and d-amphetamine (3,20), aripiprazole might have a narrow therapeutic window as a pharmacotherapy for stimulant-use disorders.

Although the present results indicate that 15 mg/day aripiprazole is safe and tolerable when combined with cocaine, an enhancement of the effects of cocaine during maintenance is not a desirable outcome for a pharmacotherapy. In addition, a clinical trial that tested 15 mg/day aripiprazole for methamphetamine dependence was terminated early because aripiprazole increased methamphetamine use compared to placebo (4). However, a large-scale clinical trial has yet to be conducted in cocaine-dependent individuals, and is needed to determine the efficacy of aripiprazole as a pharmacotherapy for cocaine-use disorders. Furthermore, aripiprazole might be effective in special populations of cocaine-dependent patients. For example, in schizophrenic patients, aripiprazole decreased the number of cocaine-positive urines (22), and in another study in patients with bipolar or schizoaffective disorder, aripiprazole reduced cocaine craving (23), suggesting that aripiprazole would be useful in cocaine-dependent individuals with co-existing psychiatric conditions. Thus, the efficacy of aripiprazole to manage cocaine dependence remains to be determined.

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Figure 1.

Peak effect dose-response functions for cocaine following maintenance on 15 mg aripiprazole (circles) or placebo (squares) for Heart Rate, subject ratings of Like Drug, Pay For and Willing to Take Again from the Drug-Effect Questionnaire (maximum score of 4) and subject ratings of Stimulated on a Visual Analog Scale (maximum score of 100). X-axis: Intranasal cocaine dose. Symbols above PLB represent data following administration of 4 mg intranasal cocaine. Brackets indicate one S.E.M. Unidirectional brackets were used for clarity.