Cocaine-Induced Cerebral Vasoconstriction Detected in Humans With Magnetic Resonance Angiography

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Context.—Clinical observations and case reports suggest that there are important cerebrovascular complications of cocaine use, but no studies have documented a direct link.

Objective.—To determine whether low-dose cocaine administration induces cerebral vasoconstriction in healthy cocaine users.

Design.—Randomized controlled trial.

Subjects.—Twenty-four healthy and neurologically normal men (mean age, 29 years) reporting median cocaine use of 8 lifetime exposures (range, 3 to >40).

Intervention.—Double-blind intravenous administration of cocaine (0.4 or 0.2 mg/kg) or placebo, with cerebral magnetic resonance angiography performed at baseline and 20 minutes following infusion.

Main Outcome Measure.—Cocaine-induced angiographic change indicative of vasoconstriction, as independently and concordantly rated by 2 reviewers blind to treatment condition.

Results.—Cocaine-induced cerebral vasoconstriction in a dose-related fashion ($P = .03$), with angiograms indicative of vasoconstriction found in 5 of 8 and 3 of 9 subjects receiving 0.4- and 0.2-mg/kg cocaine, respectively, compared with 1 of 7 subjects administered placebo. Outcome stratification by frequency of self-reported lifetime cocaine use (3-10 times, 11-40 times, or >40 times) revealed a statistically stronger dose-related effect ($P < .001$), suggesting that greater lifetime cocaine use was associated with a greater likelihood of vasoconstriction.

Conclusions.—Cocaine administration induced dose-related cerebral vasoconstriction on magnetic resonance angiograms. These changes occurred at low cocaine doses and in the absence of other risk factors, including polydrug abuse, hypertension, or cerebrovascular disease. Outcome stratification by prior cocaine use statistically strengthened the relationship between cocaine administration and vasoconstriction, suggesting that cocaine may have a cumulative residual effect in promoting cerebrovascular dysfunction.

JAMA. 1998;279:376-380

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Although the cocaine epidemic of the mid 1980s has waned, the Substance Abuse and Mental Health Administration reported that nearly 2.5 million Americans admitted occasional and 600,000 admitted frequent cocaine use in 1995.1 These statistics indicate that a large number of individuals are exposing themselves to potentially adverse health consequences associated with cocaine use, the best-documented being cardiovascular dysfunction.2-4 Historically, the frequency of major cerebrovascular abnormalities in hospital admissions associated with cocaine abuse has been relatively low (0.35%-3%).5,6 However, this frequency now appears to be on the increase. The case report literature illustrating catastrophic neurologic and cerebrovascular complications in cocaine users7-11 is rapidly growing, and the incidence of cocaine-related strokes has been characterized as reaching epidemic proportions.11 The most likely mechanism for these effects is cocaine-induced cerebral vasospasm.9,10,12 Based on the lack of vascular pathology at autopsy, cerebral vasospasm or vasoconstriction has also been suggested to occur in cocaine-associated intracranial hemorrhage.13,14 A more subtle form of cerebrovascular dysfunction found approximately 80% of the time in long-term cocaine users15-17 is the development of focal perfusion defects. These focal defects have not been associated with any significant cerebral pathologic abnormality, but have been associated with moderate to severe cognitive dysfunction.15-17 Importantly, such
perfusion defects persist during periods of cocaine abstinence17,18 as do cognitive abnormalities,19-24 suggesting that cerebrovascular dysfunction occurs and is maintained beyond the period of acute cocaine intoxication. The "clinically silent" nature of these abnormalities implies that substantial numbers of cocaine users may be affected with these defects yet remain undiagnosed. The causes of these subtle changes have not been elucidated, although cocaine-induced vasoconstriction or vasospasm has been implicated.25,26

The suggestion that cocaine-induced cerebral vasoconstriction may mediate both catastrophic and subtle clinical sequelae is supported by the observation that cocaine and its metabolites are potent cerebral vasoconstrictors in animal models.21-24 However, to our knowledge, no study to date has documented a direct relationship between cocaine administration and human cerebral vasoconstriction. A relationship cannot be ascertained from case report studies, as they include confounders such as concurrent polydrug abuse (eg, the use of cocaine plus other vasoactive substances such as heroin, alcohol, or amphetamine), the presence of vasoactive adulterants in illicit drugs,13 and potential underlying cerebrovascular disease. Additionally, wide variations in cocaine purity and self-administration procedures preclude establishment of dose-effect relationships between cocaine and cerebral vasoconstriction.

Accordingly, this prospective study was designed to evaluate whether intravenous administration of low doses of pure, pharmaceutical grade cocaine hydrochloride could induce cerebral vasoconstriction in otherwise healthy human subjects. Serial noninvasive imaging of the major cerebral arteries was conducted at baseline and 20 minutes following cocaine administration, using magnetic resonance angiography (MRA), which is highly sensitive to blood flow perturbations and has proven useful for detecting acute cerebrovascular vasospasm.27,28 Vasoconstriction results in vessel signal intensity loss at the site of and distal to the constricted region. Magnetic resonance angiography is advantageous in that it is noninvasive and does not use ionizing radiation, facilitating within-subject repeat-measures study designs. We hypothesized that intravenous cocaine administration would promote a dose-related vasoconstriction of major cerebral arteries.

METHODS

Subjects

Subjects with either no history of cocaine use or with a diagnosis of cocaine abuse or dependence (according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition27 criteria) were excluded from this study. A group of 24 healthy, medically and neurologically normal men aged 29 (5) years (mean [SD]) who reported occasional cocaine use (median, 3; range, 0 to >40 lifetime exposures, primarily via insufflation) was selected for study participation. Subjects provided written informed consent with McLean Hospital Institutional Review Board approval. Subjects underwent a complete physical and neurological examination, including electrocardiogram and blood work, prior to study and provided a medical history including estimates of illicit drug usage (Table 1).

On the study day, subjects provided breath and urine samples to detect recent alcohol or illicit drug use. Breath samples were analyzed with a breathalyzer (Alco Sensor III Breathalyzer, Intoximeters Inc, St Louis, Mo). Urine samples were analyzed for the presence of cocaine, amphetamines, phencyclidine, opiates, barbiturates, benzodiazepines, and tetrahydrocannabinol with a urinary immunoassay system (TriAge Test, Biosite Diagnostics, San Diego, Calif). All subjects had negative breath alcohol and urine screens. Each subject had an 18G angiocath inserted into a vein overlying the antecubital fossa for cocaine or placebo administration. Subjects were fitted with noninvasive cardiovascular monitoring equipment (In Vivo Research, Inc, Orlando, Fla) including 4-lead electrocardiogram, blood pressure cuff, and pulse oximeter, which provided continuous monitoring of the electrocardiogram, blood pressure, and heart rate.

Magnetic Resonance Scanning

Magnetic resonance imaging was conducted with a clinical magnetic resonance scanner (1.5 Tesla Sigma Scanner, General Electric, Milwaukee, Wis). T1-weighted sagittal localizer images (repetition time [TR]/echo time [TE]: 600/19 msec) were used to position MRA imaging sets. Angiogram imaging sets of 60 axial images were collected with the 3-dimensional time-of-flight sequence, with magnetization transfer, flow compensation and saturation imaging options. The following acquisition parameters were used: TR/TE, 48/6.9 msec; flip angle, 20°; field of view, 19 cm; matrix, 256×192; slice thickness, 1.2 mm; 1 NEX [number of excitations]; and imaging time, 7.5 minutes. Each image set produced a single axial maximum intensity projection image that was analyzed for the presence of vasoconstriction.

Drug Administration

Each subject received a single drug challenge. Cocaine (0.2 or 0.4 mg/kg) or placebo was administered by slow intra-venous injection into the antecubital vein catheter over 1 minute. These doses were chosen as they have been shown to be safe in other human studies.29-30 The slow 1-minute infusion was performed to minimize the risk of adverse effects. No adverse effects were noted in any of the subjects in this study. Drug doses were prepared by the hospital pharmacy such that research staff remained blind to the experimental condition. Drugs were administered in a double-blind manner in this randomized controlled trial, with 1 exception: the attending physician was aware when cocaine was to be administered for precautionary measures. Seventeen minutes after drug administration, a postdrug 3-dimensional time-of-flight series was initiated, with a midpoint of the imaging sequence occurring 20 minutes after drug administration.

Image Analysis

Each image set was analyzed for the presence or absence of vasoconstriction, when compared with baseline. Two expert raters, blinded with regard to study drug administration, independently analyzed the 24 image sets. Prior to analysis, the 2 raters agreed on criteria that would be used to determine alterations between baseline and postdrug images. These criteria included subtle image differences, such as changes in the caliber of moderate- and large-sized arteries and focal narrowing or complete signal loss in a major arterial structure. Image sets were scored as unchanged, ambiguous, or altered. Concordance was established when both raters agreed in their independent scan ratings. A weighted κ statistic27 of 0.64 for interrater agreement showed a very high degree of between-rater concordance (P=.003, 2-sided; unweighted κ=.70, P<.001).

Table 1.—Lifetime Self-reported Illicit Drug Use*

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Lifetime Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>39 (5)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Opiates</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Sedatives</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

*Data shown are mean (SE) using average values of reporting ranges (see below) as the numerical index of drug use. The exposure ranges used are deliberately broad (0-4 times, 5-10 times, 11-39 times, and >40 times). This helps to account for factors that preclude accurate determination of absolute drug use, even in cooperative subjects. These include variable purity of street drug, variable route and amount of administration per "exposure," the possibility that some subjects will not be truthful in reporting prior drug use, and the possibility that acute and/or chronic memory deficits in some study subjects affect reporting accuracy. Based on these reporting methods, illicit drug use was statistically equivalent across the 3 dosing groups for all substances with the exception of marijuana.1

1The high cocaine dose group reported 46 (4) and the placebo dose group reported 27 (8) lifetime marijuana exposures (P=.03).
Table 2.—Effects of Cocaine or Placebo Administration on Cardiovascular Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=7)</th>
<th>0.2-mg/kg Cocaine (n=9)</th>
<th>0.4-mg/kg Cocaine (n=8)</th>
<th>ANOVA</th>
<th>F1,21</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Peak +20 min</td>
<td>Baseline Peak +20 min</td>
<td>Baseline Peak +20 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>63 (2) 69 (3)†</td>
<td>64 (2)†</td>
<td>62 (2)†</td>
<td>64 (3)†</td>
<td>98 (5)†</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>67 (2) 105 (4)§</td>
<td>85 (2)§</td>
<td>67 (2) 105 (4)§</td>
<td>98 (5)†</td>
<td>11.6</td>
<td>.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>129 (8) 142 (7)†</td>
<td>133 (8)§</td>
<td>131 (5) 152 (6)§</td>
<td>137 (5)‡</td>
<td>117 (4)</td>
<td>.01</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>62 (3) 71 (2)§</td>
<td>66 (4)</td>
<td>68 (3) 89 (4)§</td>
<td>78 (4)†</td>
<td>74 (3)§</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Data shown are mean (SE). Repeated-measures analysis of variance (ANOVA), testing for dose effect 20 minutes after drug administration vs baseline values, bpm indicates beats per minute, and BP, blood pressure.
†Significantly different from baseline within dose group (P<.01, paired t test).
‡Significantly different from peak within dose group (P<.05, paired t test).
§Significantly different from baseline within dose group (P<.001, paired t test).
¶Significantly different from 0.2-mg/kg dose group baseline (P<.05, paired t test).
©Significantly different from placebo dose group baseline (P<.05, paired t test).

Subjective Effects

The subjective effects of drug administration were assessed using a modified visual analog scale. Each subject rated how “good,” “bad,” “high,” and “euphoric” they felt as well as how much they “craved cocaine.” This rating occurred at baseline and at 5 minutes after drug administration. This latter time point corresponds to the approximate time of peak subjective effects of cocaine following intravenous administration.

RESULTS

Baseline cardiovascular parameters were normal in all subjects, with heart rate averaging 66 (2) beats per minute (mean [SE]), and systolic and diastolic blood pressures averaging 126 (3) and 68 (2) mm Hg, respectively. Slight increases in heart rate and systolic and diastolic pressures were observed in the placebo group (Table 2) and were attributed to expectancy effects. Both cocaine doses elevated heart rate for the duration of the experiment, with peak increases in heart rate, systolic, and diastolic pressures (Table 2) occurring approximately 6 to 10 minutes following drug administration. Twenty minutes after cocaine or placebo administration, at the midpoint of the MRA acquisition, heart rate and diastolic pressure remained elevated in all subjects administered cocaine; systolic pressure remained elevated in subjects administered 0.4-mg/kg cocaine (Table 2). The 20-minute cardiovascular values were reduced with respect to peak values (Table 2). An overall dose effect of cocaine (repeated-measures analysis of variance [ANOVA]) was detected for heart rate and diastolic pressure at the 20-minute time point (Table 2).

Image analysis revealed that all baseline images were normal. However, following drug administration, a relationship between the cocaine dosage administered and the incidence of vasoconstriction was found. Raters determined that 5 of 8 subjects who received 0.4 mg/kg cocaine experienced angiographic alterations from baseline images indicative of cerebral vasoconstriction. These ranged from subtle differences in arterial caliber to more significant alterations, including focal narrowing or complete signal loss from a major arterial structure. These alterations were detected in the posterior cerebral artery, the middle cerebral arteries (Figure), vertebrobasilar arteries, and the anterior and posterior communicating arteries. It should be noted that the communicating arteries often reflect changes in relative regional volume flow in the anterior, middle, and posterior cerebral arteries, or even in individual branches of these vessels. Thus, alterations in the anterior and posterior communicating arteries may or may not be due to a direct vasoconstrictive effect of cocaine. Three of 9 subjects who received 0.2-mg/kg cocaine had angiographic alterations in several arteries including the anterior communicating arteries and the posterior and middle cerebral arteries. One of 7 subjects who received placebo was ruled to have an altered postplacebo MRA scan. This is attributed to expectancy effects and may be associated with the brief but significant increment in cardiovascular function noted in the placebo group (Table 2). Table 3 shows the observed classification of angiogram results stratified by cocaine dosage for all image sets. Statistical analysis of concordantly rated scans, using a linear-by-linear association model for the ordered categories of unchanged, ambiguous, and altered, indicated a significant association of increasing prevalence of altered scans with increasing cocaine dose (P=.03, 1-sided). When discordantly rated scans were included, the significance of the association decreased slightly (P=.06). These findings demonstrate an apparent relationship between cocaine administration and altered MRA scan; moreover, this effect appears to be dose related. A stratified analysis of this small sample by frequency of self-reported lifetime cocaine use (3-10 times, 11-40 times, or >40 times) revealed a statistically stronger dose-response relationship (P<.001), suggesting that prior cocaine use may have a cumulative effect in promoting angiographic changes indicative of vasoconstriction.

The subjective reporting data were analyzed with a repeated-measures ANOVA for the effect of time (eg, postdrug vs predrug ratings). Subjects reported feeling significantly more “high,” “euphoric,” and “good” after drug administration (F1,21 = 21.3, P<.001) and reported significantly more cocaine “craving” after cocaine drug administration (F1,21 = 8.2, P<.001). Additionally, a dose-effect relationship between cocaine and “high” ratings was found (F2,21 = 12.2, P<.001). These data document a rapid effect of cocaine consistent with the intravenous route of administration.

The study design precluded direct measurement of plasma cocaine levels in this experiment. However, we have obtained plasma cocaine levels by gas chromatography/mass spectrometry analysis from comparable subjects administered cocaine by identical protocols. Peak plasma cocaine levels of 230 (10) and 90 (10) ng/mL (mean [SE]) were found 6 to 8 minutes following intravenous administration of 0.4-mg/kg (n=3) and 0.2-mg/kg (n=6) doses of cocaine, respectively. Plasma cocaine levels of 180 (30) and 80 (10) ng/mL were found at 20 minutes after administration, corresponding to the midpoint time of the present MRA acquisition, following 0.4- and 0.2-mg/kg cocaine doses, respectively. These values and their time course closely parallel those published in a recent report of the venous plasma cocaine level time course following intravenous cocaine administration.

COMMENT

These results are the first to document that intravenous administration of a relatively low dose of cocaine to otherwise healthy humans can induce angiographic changes indicative of cerebral vasoconstriction. This finding suggests that low cocaine doses are sufficient to induce cerebrovascular dysfunction. The data also are suggestive of a dose-effect relationship between cocaine and vasoconstriction. It is...
Currently unclear whether simple extrapolation from these findings to predict the occurrence of cerebral vasconstriction in illicit cocaine abusers is appropriate. However, if cerebral vasconstriction is related to plasma cocaine concentration, which peaks at substantially higher levels in naturalistic cocaine abuse compared with levels found with the cocaine doses used in this study, then moderate to heavy illicit cocaine users may experience a substantial incidence of cerebral vasconstriction. As cerebral vasconstriction has been linked to hypoperfusion and persistent hypoperfusion has been associated with neuronal dysfunction, the current findings imply that repetitive moderate to heavy cocaine use may be associated with neuronal damage.

**Cumulative Effects of Cocaine and the Cause of Chronic Cocaine-Induced Brain Dysfunction**

Although it is assumed that chronic cocaine abuse is requisite to produce persistent perfusion defects and cognitive dysfunction, it is currently unclear what threshold level of cocaine exposure results in these conditions. The cognitive dysfunction observed in long-term cocaine abusers is related to amount of cocaine used, suggesting a cumulative residual effect of cocaine on brain function. Our study documents an apparent relationship between prior cocaine use and the propensity to experience vasconstriction, suggesting that cocaine may have a cumulative effect in producing cerebrovascular dysfunction in addition to its acute vasconstrictive effect. While additional studies with larger subject numbers will be needed to confirm this relationship, the current data suggest that the incidence of cocaine-induced cerebral vasconstriction may be increased in individuals who escalate from occasional to regular cocaine use.

**Study Limitations**

This study was conducted with a single-dose challenge at a single time point following cocaine administration. The single-dose challenge design is a limited model for the determination of dose-effect relationships between cocaine and cerebral vasconstriction. This design also precludes analysis of the time dependence of cocaine-induced vasconstriction. Because cocaine-induced vasconstriction is a transient phenomenon and because our time frame for its detection was short, it is conceivable that more subjects experienced vasconstriction than detected in the current study. Additionally, we are unable to address whether cocaine or its metabolites, some of which are potent vasconstrictors, mediate vasconstriction. Cocaine metabolites may play an important role in inducing delayed cerebral vasconstriction, because their levels gradually increase over several hours, and in extreme cases persist for up to several weeks. Thus, cocaine metabolites may trigger prolonged cerebral vasconstriction associated with decreased cerebral perfusion. Further, we cannot rule out the possibility that cocaine-induced increments in cardiovascular function may contribute to cerebral vasconstriction. The current findings warrant further MRA studies using within-subject repeated-measures models to confirm the dose-effect relationship between cocaine and cerebral vasconstriction, as well as to evaluate temporal patterns of cocaine- and metabolite-induced cerebral vasconstriction.

The current study used intravenous cocaine administration as the drug delivery method, while intranasal administration and smoking of the alkaloidal form “crack” are the more common forms of administration. The mode of cocaine administration has been suggested to be related to cerebrovascular effect, with the intravenous route leading to hemorrhagic strokes and “crack” smoking leading to both ischemic and hemorrhagic stroke. It is unclear from our data whether a different form of cocaine or a different route of administration would produce a dissimilar rate or severity of vasconstriction. However, our finding of an apparent dose-effect relationship between cocaine and vasconstriction suggests that once a sufficient plasma cocaine concentration is achieved, cerebral vasconstriction may occur.

A final limitation of this study was the reliance on a qualitative, rather than a quantitative, method of angiogram evaluation. However, the two raters achieved a high degree of concordance, indicating a high degree of interrater reliability. We thus conclude that these data are suggestive of a dose-effect relationship between cocaine and cerebral vasconstriction. These results underscore the risks of single doses of cocaine in promoting cerebrovascular abnormalities, particularly in individuals with other risk factors. The data also strongly suggest that there is an increased risk of cerebrovascular dysfunction in individuals who are frequent or long-term cocaine users, and that this dysfunction may be progressive. Together, these findings highlight the potential dangers of cocaine use on cerebrovascular function and document the importance of developing effective prevention strategies as well as treatments that protect against cocaine-induced vascular dysfunction.
References


