Regional Cerebral Blood Flow Improves with Treatment in Chronic Cocaine Polydrug Users

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Brain perfusion is abnormal in chronic cocaine users. To determine whether these perfusion abnormalities are reversible following treatment, we studied 10 cocaine-dependent polydrug users with ^{99m}Tc-HMPAO SPECT 2 to 3 days after admission to an inpatient treatment facility and at 7 to 8 days and 17 to 29 days after abstinence from drugs. The patients also received buprenorphine, an opioid mixed agonist-antagonist, beginning 10 days after admission and continuing to the end of the study. Imaging began 10–15 min after injection of ^{99m}Tc-HMPAO (20 mCi) using an annular gamma camera system. MRI was performed during hospitalization using a 1.5 Tesla system. SPECT and MRI were merged and five axial SPECT slices centered at the level of the basal ganglia were selected for analysis. Activity ratios were derived for cortical regions relative to cerebellar activity and were corrected for linearity with respect to regional cerebral blood flow. The cortical regions were classified as abnormal (activity ratio < 0.6), borderline (0.6–0.72) and normal (> 0.72) based on the results of the first SPECT study. In abnormal zones, regional cerebral blood flow (rCBF) increased 11.0% ± 9.0% at 7 to 8 days and 23.8% ± 9.4% at 17 to 29 days after initiation of treatment. The increase in rCBF was 4.8% ± 7.1% (7 to 8 days) and 11.1% ± 8.0% (17 to 29 days) in borderline cortex and decreased 2.9% ± 6.3% (7 to 8 days) and increased only 2.7% ± 13.4% (17 to 29 days) in normal cortex. The increase in rCBF did not vary significantly by location. The perfusion defects observed in chronic cocaine polydrug users are partially reversible with short-term abstinence and buprenorphine treatment.

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The cocaine abuse epidemic continues both in the general population (*1–3*) and among heroin-dependent persons, including those in methadone treatment programs (*4–6*). Cocaine abuse is associated with a number of adverse medical complications, including myocardial infarction, ventricular arrhythmias and stroke (*7–9*). While catastrophic neurovascular damage following subarachnoid and intracerebral hemorrhage and infarction is uncommon, brain perfusion defects occur with high frequency in polydrug abusers who are chronic cocaine users (*10*) and abnormal brain perfusion patterns are often indistinguishable from those in early AIDS dementia complex (*11*). Recent estimates indicate intravenous drug use accounts for 10%–60% of new AIDS cases (*1*). Dependence on both intravenous cocaine and heroin may increase the risk for AIDS through needle sharing and through the combined immunosuppressive effects of each drug (*12–15*). Many medical disorders may be exacerbated by the combined use of cocaine, heroin and other drugs (*16,17*).

The goal of this study was to determine whether perfusion defects in chronic cocaine polydrug users are reversible. High-resolution ^{99m}Tc-HMPAO SPECT was used to assess regional cerebral blood flow (rCBF) during early, sustained and protracted abstinence from heroin and cocaine self-administration.

METHODS

Study Population

Ten males diagnosed with concurrent heroin and cocaine dependence (DSM-III-R criteria) were studied under controlled inpatient clinical ward conditions. Subjects were recruited through advertisements in local newspapers. All subjects were interviewed and examined by a physician and laboratory studies were performed to rule out medical illness. None exhibited evidence of cardiovascular or neurologic disease and all subjects tested negative for the HIV antibody. Drug histories were obtained via: (1) a medical history interview with a physician; (2) written drug history questionnaires; and (3) the orally administered Structured Clinical Interview for DSM-III-R. To insure consistency, these three procedures were performed or reviewed by the examining physician. The mean age of the subjects was 32.6 ± 1.1 (s.d. range 26–39 yr) and their mean weight was 72.4 ± 2.7 kg (range 61.4–86.4 kg).

All subjects met DSM-III-R Axis I diagnostic criteria for cocaine dependence. They reported an average of 9.8 ± 1.7 yr of cocaine use (range 3–19 yr) and an average use of 10.4 ± 3.9 g/wk (range 1–37 g/wk). All subjects used cocaine intravenously; three subjects also freebased and four subjects also inhaled cocaine. All subjects met DSM-III-R diagnostic criteria for opioid dependence. They reported an average of 9.6 ± 2.2 yr of opioid use (range 2–19 yr). The average amount of heroin used

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per week was 59.5 ± 10.4 "bags" (range 3.5–122 "bags"/wk). Nine subjects used alcohol currently and met criteria for current alcohol abuse or dependence. Three subjects met DSM-III-R criteria for current abuse of or dependence on cannabinoids and three subjects met DSM-III-R criteria for current abuse of or dependence on sedatives.

On the day of admission, urine drug screening was positive in nine of the ten patients, with evidence of cocaine metabolites in seven patients, morphine in seven, cannabinoids in two, codeine in three, benzodiazepine in one, ethyl alcohol in one, propoxyphene in one and methadone in one patient. All subjects received methadone for heroin detoxification on admission to the inpatient treatment facility. No drugs were used for alcohol detoxification. During this period, no subject showed any signs or symptoms of alcohol withdrawal such as tachycardia, nausea, vomiting, tremulousness, psychomotor agitation or increased deep tendon reflexes. Following detoxification, subjects were enrolled into the study.

Subjects were abstinent from cocaine and heroin use during the inpatient study and drug-free status was verified with urine drug screens. These men were given daily treatment with sublingual buprenorphine, an opioid agonist-antagonist analgesic (*18–20*), during the 10th through 29th day of the inpatient clinical trial. Six patients received 2–4 mg/day and four patients received 8 mg/day of buprenorphine.

Imaging Protocol

Brain perfusion SPECT imaging was performed on three occasions: on study days 2–3 (Study 1), on study days 7–8 (Study 2) and on study days 17–29 (Study 3).

Imaging began 10–15 min following the intravenous injection of 20 mCi of ^{99m}Tc-HMPAO (Ceretec, Amersham, Ltd., Amersham, England). Data were acquired for 30 min on an ASPECT system (Digital Scintigraphics, Inc., Boston, MA) in 120 projections with a 360° rotation of the collimators (*21*). Two pulse-height analyzer windows were employed, one set at 140 ± 14 keV and one set to acquire scatter information from 112–126 keV. The combined set of projections was then calculated by subtracting 90% of the scatter projections and prefiltered to remove the forward scatter component from the photopeak projections using a Butterworth filter (cutoff = 1.05 cycles/cm; power factor = 20). Data were reconstructed in the axial plane parallel to the orbitomeatal line. The reconstructed slices were attenuation-corrected and displayed on a 128 × 128 matrix (1.67 × 1.67 mm pixel size) as a set of 15 slices (8.0 mm slice thickness).

Axial and sagittal magnetic resonance images were acquired using a 1.5 Tesla Signa System (General Electric Co., Milwaukee, WI). Sagittal localization images were obtained with a standard spin echo technique (TR = 600 msec/TE = 20 msec). Axial and sagittal T1-weighted images were obtained with spin-echo pulse sequences (TR = 600 msec/TE = 20 msec/nex = 1) with a slice thickness of 3 mm, a 256 × 192 matrix and a 24-cm field of view. T2-weighted axial images were obtained with spin-echo pulse sequences (TR = 3000 msec/TE = 30, 80 msec/nex = 0.5) with a slice thickness of 3 mm.

Visual Analysis

SPECT images were interpreted visually using a method that we have previously described (*22*). The color display level was individually adjusted for each patient so that the central area of the cerebellum was white (greater than 90% of the maximum activity of the slice), thus normalizing the entire dataset to the ^{99m}Tc-HMPAO activity in the cerebellum. Datasets were classified as abnormal based on the appearance of reconstructed cortical activity that was less than 60% of the maximum activity (absence of white, yellow or red in an area of cortex on two or more slices). Image sets were interpreted independently by two readers as to whether the studies were normal or abnormal and whether perfusion improved, deteriorated or did not change between Studies 1 and 3. Discrepancies were resolved by consensus.

Quantitative Analysis

In order to compare comparable regions, the three SPECT datasets were registered with the MR image (*23*). Brain surface contours were drawn from each MR axial image and defined a three-dimensional model of the brain surface. Brain surface contours were also drawn for the ^{99m}Tc-HMPAO ASPECT axial images. The fit, or interscan coordinate transformation (translation, rotation and rescaling), was calculated iteratively until the MRI and SPECT contour maps coincided maximally.

The axial MR images which best defined the basal ganglia were identified and the corresponding axial image from the first SPECT study (Study 1) was selected as the midcerebral slice. The two contiguous slices above and below the midcerebral slice were also selected. Each slice was 8 mm thick. Cortical regions of interest (ROIs) were selected from each slice. Between 35 and 40 ROIs were drawn over the cortex manually on the images generated from Study 1 (6–8 regions per slice). The regions measured 8.3 mm in width and 10.0–33.4 mm in length. In abnormal and borderline zones, the ROI boundaries were drawn to conform to the boundaries of the cortical perfusion defects as determined by visual inspection. ROIs were positioned over anterior, posterior, frontal, temporal, parietal, lateral, occipital and primary visual cortex. The ROIs were then electronically superimposed on corresponding images from Studies 2 and 3. In addition, two ROIs were placed over the right and left basal ganglia (caudate nucleus, globus pallidus and putamen) using the MR axial slice which best defined these structures. The ROIs were then transferred to the corresponding axial SPECT images from Studies 1, 2 and 3. Brain regions were classified by location (anterior and posterior frontal, temporal and parietal cortex) and regional activity ratios were calculated using the following procedures. A transaxial slice was selected midway through the vertical axis of the cerebellum and an activity midpoint was determined by creating a vertical count profile through the cerebellum to define the slice that corresponded to peak cerebellar activity. A ROI incorporating the gray matter of the cerebellar hemispheres was drawn manually on the axial slice. For each cortical ROI, the activity per pixel was normalized by the activity per pixel in the cerebellum for that study and corrected for linearity with rCBF using the formula: $R_{cor} = \alpha R(1 + \alpha - R)$, where R_{cor} is the corrected blood flow ratio, $\alpha = 2$, and R is the cortical-to-cerebellar activity ratio (*24–27*). Regions with corrected cerebral-to-cerebellar ratios < 0.6 were classified as abnormal, ratios between 0.6–0.72 were considered borderline and ratios > 0.72 were considered normal (based on previous data derived from normal subjects, chronic cocaine polydrug users (*10*) and patients with Alzheimer's disease (*22,28*)). For each patient, the average change in rCBF was calculated between Study 1 and Study 2 and between Study 1 and Study 3 for regions where rCBF was abnormal, borderline and normal on Study 1.

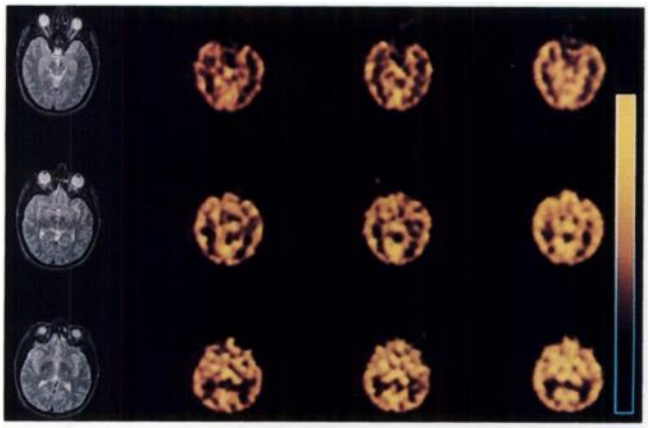

FIGURE 1. Normal MRI (column 1) in a cocaine polydrug user. Cerebral perfusion was abnormal at Study 1 (column 2) with multiple focal cortical defects on all three axial images of the ^{99m}Tc-HMPAO SPECT study. There was no significant improvement in perfusion by Study 2 (column 3). At Study 3 (column 4), cortical and striatal perfusion is improved with complete or partial fill-in of the previous perfusion defects. Each row represents the same anatomical plane as derived from the merged MRI-SPECT dataset. Rows 1 and 2 are 18 and 9 mm below the central slice at the mid-level of the basal ganglia (Row 3).

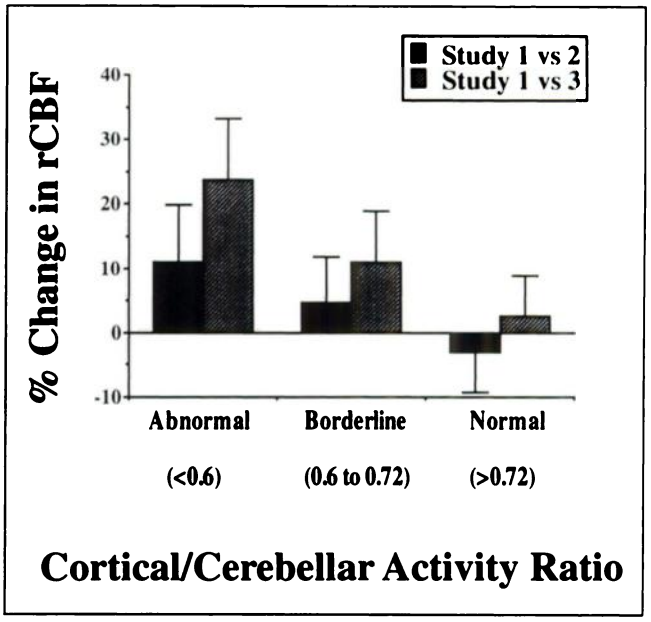

FIGURE 2. Change in rCBF at 7–8 days and 17–29 days after treatment.

The data were analyzed using the Student-Neumann-Keuls test for multiple comparisons. Dispersion about the mean was described as ±1 s.d.

RESULTS

Brain perfusion SPECT was abnormal on visual assessment in all 10 patients within 3 days of admission (Study 1). After 17–29 days of treatment, perfusion improved in eight patients, with a more uniform distribution of the tracer throughout the cortex and a reduction in the intensity of the perfusion defects (Fig. 1). In two patients, there was a discrepancy between the readers in the visual interpretation of the images (no changes versus improved perfusion). All subjects had normal MRI studies.

Upon quantitative analysis, cortical rCBF increased in abnormal zones by 11.0% ± 9.0% ($q = 3.66$, $p < 0.05$) between Studies 1 and 2 and by 23.8% ± 9.4% ($q = 7.50$, $p < 0.01$) between Studies 1 and 3 (Fig. 2). Cortical rCBF increased 4.8% ± 7.1% ($q = 2.77$, p = ns) (Studies 1 and 2) and 11.1% ± 8.0% ($q = 6.50$, $p < 0.01$) (Studies 1 to 3) in borderline regions and fell 2.9% ± 6.3% (p = ns) (Studies 1 and 2) and increased only 2.7% ± 13.4% (p = ns) (Studies 1 to 3) in normal cortex. The increase in cortical rCBF after treatment was significantly greater in abnormal zones compared to borderline zones between Studies 1 and 3 ($q = 3.78$, $p < 0.05$) and in abnormal zones compared to normal zones at all times ($q = 5.80$, $p < 0.01$ between Studies 1 and 2; $q = 6.31$, $p < 0.01$ between Studies 1 and 3). There was no difference in the increase in cortical rCBF to abnormal regions in Study 3 in the patients who received buprenorphine 8 mg/day (24.6% ± 6.0%, n = 4) and 2–4 mg/day (23.2% ± 12.8%, n = 6).

Group mean rCBF in abnormal cortex was 59.1% of flow in normal cortex at Study 1 and increased to 71.3% of normal perfusion at Study 3 ($p < 0.01$). In borderline cortex, regional blood flow was 74.2% of normal flow at Study 1 and increased to 80.3% of normal flow at Study 3 (p = ns). All patients showed an increase in rCBF in abnormal regions between Study 1 and Study 3, with a range of 11.2%–37.3%.

The increase in cortical cerebral blood flow did not vary significantly by brain region location. The change in rCBF from Study 1 to Study 2 was 4.3% ± 13.8% in the anterior frontal cortex, 8.8% ± 14.1% in the posterior frontal cortex, 13.3% ± 13.0% in the temporal cortex and 13.5% ± 17.1% in the parietal cortex. The change from Study 1 to Study 3 was 18.5% ± 12.6% (anterior frontal), 23.9% ± 14.9% (posterior frontal), 24.5% ± 19.1% (temporal) and 25.0% ± 14.6% (parietal cortex). The increase in rCBF to the basal ganglia, however, was only 8.4% ± 12.9% from Study 1 to Study 2 and 9.2% ± 13.7% from Study 1 to Study 3 (p = ns).

DISCUSSION

Cocaine is a potent vasoconstrictor and results in alterations in regional blood flow. Vasoconstriction has been reported in the coronary arteries in association with cocaine administration (*7*) and cocaine has been reported to cause elevated blood pressure and heart rate as well as focal cerebral lesions such as intracranial or subarachnoid hemorrhage and infarction (*29*).

Chronic cocaine use also results in generalized multifocal alterations in rCBF which occur without underlying structural damage (*10,30,31*). With high-resolution imaging, multiple small and moderate perfusion defects have

been reported in the cortex, with altered blood flow to the basal ganglia and a generalized reduction in cerebral uptake of radiotracers that distribute proportionately to blood flow (*12*). Since most of these patients had normal structural findings on CT and MRI, the perfusion defects are not due to underlying infarction and hemorrhage. Nevertheless, preliminary reports have suggested that these changes in cerebral blood flow are not responsive to short-term withdrawal of drugs and may therefore be permanent sequelae of cocaine use (*32,33*). Our study indicates a substantial improvement in perfusion to cortical areas seen in cocaine polydrug abusers with a 45% increase in blood flow after three to four weeks of abstention. However, rCBF did not completely return to normal in 9 of the 10 patients. These findings of normal structure and partially reversible function in cocaine polydrug users suggest that the cortical perfusion defects may be due to vasoconstriction, a phenomenon associated in the heart and other organs with cocaine use (*7*). The failure of basal ganglia blood flow to increase as much as cortical flow is consistent with the findings of Volkow et al. that glucose metabolism and dopamine binding in the basal ganglia and orbital frontal cortex did not increase with drug withdrawal (*34*). This suggests that these areas may be affected by changes in receptor function rather than by vasoconstriction.

Buprenorphine, an opioid mixed agonist-antagonist, significantly suppresses cocaine self-administration by rhesus monkeys (*35–37*) and human polydrug users (*38,39*). Because the dose of buprenorphine did not affect rCBF, it is likely that the duration of cocaine abstinence rather than buprenorphine treatment accounted for the increase in cerebral blood flow.

We took advantage of a number of technological advances that improved our ability to measure cerebral blood flow changes in small areas of the cortex. The ASPECT system has high spatial resolution and can separate point sources which are 7 mm apart at the center of the field of view (*21*). Furthermore, by merging the SPECT studies with MRI, it is possible to select the same region from multiple SPECT studies without the need for rigid fixation devices even when the studies are performed at intervals of days or weeks. We have reported previously an average misregistration of only 2–3 mm for deep structures such as the thalamus using this method (*23*). Misregistration for the cortex is less because the contours are drawn over the surface of the brain.

In conclusion, cocaine-induced abnormalities in rCBF improve with inpatient treatment. Consequently, the perfusion defects observed in chronic cocaine-dependent polydrug users are at least partially reversible.

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