Improved Regional Cerebral Blood Flow in Chronic Cocaine Polydrug Users Treated with Buprenorphine

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Chronic cocaine and polydrug abuse have been associated with regional abnormalities in cerebral perfusion. The authors have previously demonstrated that these abnormalities are partially reversible after drug addiction treatment with buprenorphine. This study was designed to separate the effect on cerebral perfusion of abstinence from drug use from that of buprenorphine directly. **Methods:** Fifteen cocaine- and heroin-dependent men were studied with ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) brain SPECT. The men, all part of an inpatient drug abuse treatment research program, were randomly assigned after detoxification to receive placebo or either 6 or 12 mg daily buprenorphine treatment. SPECT studies were performed at baseline, after maximum dosage was reached and after tapering off the study drug. Studies were compared visually with regard to the number and location of perfusion defects by reviewers blinded to treatment assignment. **Results:** Subjects receiving buprenorphine had a significant reduction in the number of defects per study between baseline and maximum buprenorphine dose as compared with those receiving placebo (decrease of 4 ± 5.4 versus increase of 4.8 ± 4.7, $p = 0.006$). These differences were dose-related. Improvement with buprenorphine was temporary, with return to baseline after tapering off. **Conclusion:** Buprenorphine treatment, and not abstinence from drug use alone, leads to improvement in regional cerebral perfusion abnormalities in chronic cocaine- and heroin-dependent men.

Key Words: cerebrovascular perfusion; cocaine; heroin; technetium-99m-HMPAO; buprenorphine; single-photon emission computed tomography

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The medical and neurological complications associated with cocaine and polydrug abuse are well known. Several groups in the last few years have demonstrated regional abnormalities in cerebral blood flow (CBF) and metabolism in chronic and acute cocaine use (*1–9*). The authors have previously used SPECT with ^{99m}Tc-HMPAO, a lipophilic radiopharmaceutical with rapid and stable brain uptake in proportion to cerebral perfusion (*10,11*), to demonstrate focal perfusion abnormalities, especially in anterior brain structures, in exclusively cocaine-dependent men as well as in cocaine-polydrug-dependent men (*6*). They have also shown that these perfusion abnormalities improve with treatment with the mixed opioid agonist-antagonist buprenorphine (*12*). This preliminary study left unclear, however, whether the improvement was due to buprenorphine treatment itself or abstinence from drug abuse. Because opioid antagonists such as naloxone have been shown to augment cerebral perfusion in both normal and ischemic brain (*13–21*), as well as reverse the decrement in CBF produced by opioid agonists (*22,23*), the authors sought to evaluate the effect of buprenorphine on cerebral perfusion in drug-abusing men undergoing treatment.

METHODS

Patients

Fifteen men (mean age 33.5 yr; range 25–45 yr) were enrolled in an inpatient drug abuse treatment research program after recruitment. Each patient underwent extensive medical and neurological evaluation with routine blood work, brain MRIs and HIV antibody testing all negative. Drug histories were obtained via: (a) a medical history interview with a physician; (b) written drug history questionnaires; and (c) the orally administered Structured Clinical Interview for DSM-III-R. All subjects met DSM-III-R criteria for cocaine dependence, and all subjects used cocaine intravenously. They reported an average of 9.6 ± 5.2 yr of cocaine use using an average of 3.8 ± 3.9 g/wk. All subjects met DSM-III-R criteria for opioid dependence as well, reporting an average of 9.4 ± 6.7 yr use of 8.2 ± 5.1 "bags"/day. No subject met DSM-III-R criteria for any other Axis I psychiatric diagnosis except for nicotine dependence. All aspects of the study were approved by the Institutional Review Boards of McLean Hospital and the Brigham and Women's Hospital. Written informed consent was obtained from each subject prior to each imaging procedure.

All men were admitted to an inpatient drug treatment research unit where they were maintained free of illicit drugs and were subject to random drug screening. All underwent a 6-day detoxification with methadone, followed by a 5-day drug-free period.

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TABLE 1
Comparison of Treatment Groups

	Control (n = 5)	6 mg (n = 5)	12 mg (n = 5)
Age (yr)	36.2 ± 7.6	32 ± 5.1	32.2 ± 3.4
BMI	28.4 ± 8.9	24.9 ± 1.9	23.8 ± 3.2
Duration of heroin use (yr)	7.6 ± 5.9	13.4 ± 8.6	7.1 ± 4
Amount of heroin use (bags/day)	7.8 ± 2.8	11.7 ± 6.6	5.2 ± 3.5
Duration of cocaine use (yr)	13.2 ± 4.5	8.4 ± 5.3	7.3 ± 4.7
Amount of cocaine use (g/wk)	2.95 ± 3	7.2 ± 4.6	1.3 ± 1
Baseline mean lesions/study	10 ± 5	9 ± 5.6	15 ± 5.8

No significant difference between any of the groups: Mann-Whitney U-test yields p values >0.05 for all comparisons.

After detoxification, they were randomly assigned in a double-blind fashion to one of three treatment groups: placebo, 6 mg buprenorphine or 12 mg buprenorphine. Medication was administered daily by the sublingual route and subjects were observed for adverse reactions. Doses of medication were increased daily from 1 mg on Day 1 to the maintenance dose mentioned above on Day 5. Medication was then maintained at that steady dose from Day 5 until Day 16, at which point it was tapered to zero by Day 21. Four patients, however, were maintained on the study drug, placebo or buprenorphine at their request; two received 12 mg buprenorphine, one received 6 mg buprenorphine, and one received placebo.

Imaging Protocol

Brain perfusion SPECT imaging was performed on three occasions: Day 1 (Study 1), Day 5 (Study 2) and Day 21 (Study 3). Imaging took place several hours after the early morning administration of the daily dose of the study drug. All 15 subjects had Studies 1 and 2. Twelve subjects had Study 3, and of these only two subjects were among those not tapered off the study drug.

Imaging began 10–15 min postintravenous injection of 20 mCi ^{99m}Tc-HMPAO (Ceretec, Amersham, Ltd., Amersham, England). Data were acquired for 40 min on an ASPECT system (*24*) (Digital Scintigraphics, Inc., Boston, MA) in 120 projections with a 360° rotation of the collimators using a previously described method (*6,12,24*). Data were attenuation-corrected, reconstructed in the axial plane parallel to the orbitomeatal line and in the coronal plane. The reconstructed slices were displayed on a 128 × 128 matrix (1.67 × 1.67 mm pixel size) as a set of twenty 5-mm thick axial slices and as a set of twenty 5-mm thick coronal slices.

Axial magnetic resonance (MR) images were acquired using a 1.5 Tesla Signa System (General Electric Co., Milwaukee, WI). Spin-echo, T1-weighted (TR = 600 msec/TE = 20 msec) and T2-weighted and proton density (TR = 3000 msec/TE = 80,30 msec/NEX = 0.5) 3-mm thick slices were obtained with a 256 × 192 matrix and a 24-cm field of view.

Image Analysis

Transaxial and coronal SPECT images for each study were displayed on a computer terminal. The color display level was adjusted for each study so that the central area of the cerebellum was white (greater than 90% of the maximum activity of the slice), thus normalizing the entire study to the ^{99m}Tc-HMPAO activity in the cerebellum. Each study was analyzed for defects in perfusion visible on at least two (axial) or three (coronal) contiguous slices. Defect determination was entirely visually guided, without automation, and a defect was defined as an area of at least 0.5 cm in diameter in which total activity was less than 60% of maximum, as indicated by a color change from orange to blue. Defects were considered small if they were between 0.5 and 1 cm in diameter, medium if between 1 and 2 cm and large if greater than 2 cm. Total number and size of distinct defects were determined for each region (frontal, temporal, parietal, occipital, basal ganglia, thalamus, cerebellum) of each study and recorded on a database. Images were interpreted by three radiologists, each of whom was blinded to the identity of the treatment group designation and the order of each subject's studies. Discrepancies were resolved by consensus or by agreement of two of three readers.

MR studies were interpreted by a single neuroradiologist who was likewise blinded to the treatment group designation of each subject.

Statistical Analysis

The number of defects were treated in a weighted fashion: small defects received a weighting of 1, medium defects 2 and large defects 3. The number of these weighted defects was then compared across treatment groups (different doses of buprenorphine and placebo) using the Mann-Whitney U-test, as were differences in covariates among treatment groups. Because each of the subjects served as his own control to reduce the effect of intersubject variation, the change in the number of defects per study through time, rather than absolute number of defects, was used for all comparisons. All tests and reported probability values are two-sided. Dispersion about the mean is reported as ±1 s.d.

RESULTS

No significant differences were found among the treatment groups with respect to any of the following covariates: age, body mass index (BMI), amount of cocaine and heroin use, duration of cocaine and heroin use and alcohol use (Table 1). All MR studies were interpreted as normal.

Comparing the weighted number of defects at baseline (Study 1) and after 5 days of escalating buprenorphine therapy (Study 2), subjects receiving buprenorphine had an average decrease of 4 ± 5.4 defects per study, while those receiving placebo had an average increase of 4.8 ± 4.7 defects per study ($p = 0.008$). A comparison of buprenorphine dose revealed a dose-response relationship. Subjects receiving 6 mg buprenorphine had no change (± 1.8) in the number of defects per study, significantly different from placebo ($p = 0.04$), while subjects receiving 12 mg had an average decrease of 8 ± 4.6 defects per study, which is also significantly different from the placebo group ($p = 0.009$).

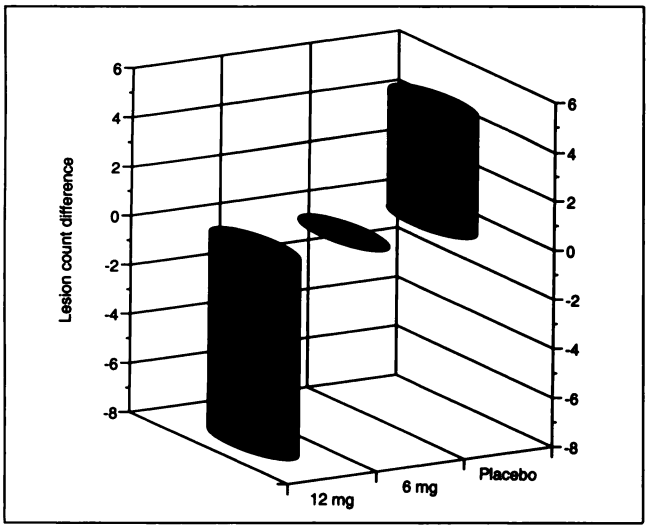

FIGURE 1. Mean difference in lesion count between Studies 1 and 2 by treatment group. Placebo treatment is associated with a slight increase in the number of lesions per study, whereas 12 mg buprenorphine are associated with a marked decrease.

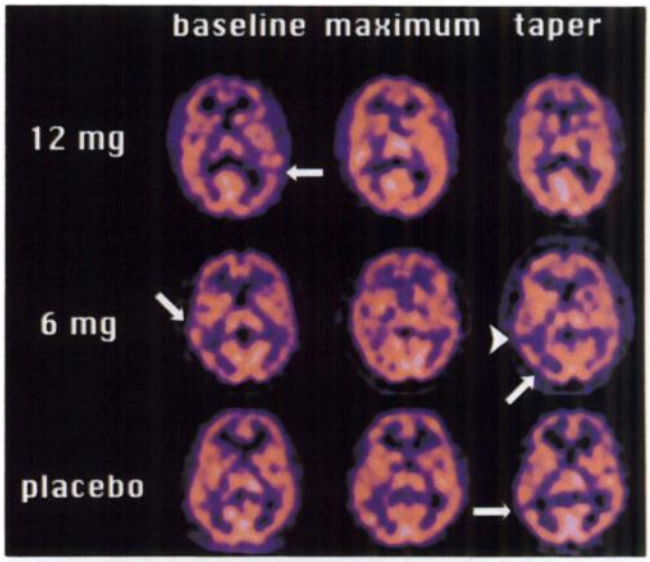

FIGURE 2. Comparision of representative brain SPECT images of cocaine-dependent men in each of three treatment groups at three separate time points: baseline (Study 1), maximum drug treatment (buprenorphine or placebo, Study 2) and after study drug taper (Study 3). A comparable midcortical slice includes the basal ganglia, thalamus, frontal, temporal, parietal and visual cortex. The 12-mg study shows marked improvement in perfusion, while the 6-mg study shows mild improvement. The placebo study shows no improvement. Following taper, all groups show poorer perfusion. Arrows indicate representative small perfusion defects and the arrowhead indicates a moderately sized defect.

A direct comparison of 6 mg to 12 mg buprenorphine also achieved statistical significance ($p = 0.047$) (Fig. 1). Analysis using nonweighted defect data did not alter these results significantly.

A comparison was also made between the number of defects at baseline (Study 1) and after tapering off buprenorphine (Study 3). There was no significant difference between subjects who had received buprenorphine and those who had received placebo (average decrease of 2 ± 7.9 defects per study versus average decrease of 1 ± 6 defect per study, $p = 0.93$). Comparing doses of buprenorphine did not affect these results. Those receiving 6 mg had an average increase of 0.6 ± 6.3 defects per study ($p = 0.54$) and those receiving 12 mg had an average decrease of 6.3 ± 9.5 defects per study ($p = 48$) as compared to placebo (Fig. 2).

DISCUSSION

Subjects treated with buprenorphine had a significant decrease in the baseline number of SPECT perfusion defects 5 days after beginning treatment with buprenorphine as compared to placebo. In addition, the decrease in perfusion defects was dose-related, with those receiving 12 mg having significantly more reduction in defect number than those receiving 6 mg. As the different dosage groups did not differ significantly in terms of number of baseline defects, baseline differences do not appear to underlie these findings.

By comparing the baseline study (Study 1) with the study following discontinuation of buprenorphine (Study 3), no difference was detected in the number of defects per study between either dose of buprenorphine and placebo following drug taper. This reversibility, along with the dose response relationship, strongly indicates that buprenorphine, rather than abstinence, is responsible for the observed improvement in cerebral perfusion.

The effect of opioids, and their agonists and antagonists, on CBF and metabolism has been studied in detail in the normal and ischemic brain. Several groups have found that opioids, such as morphine or heroin, decrease global or regional CBF after acute administration in normal laboratory animals (*20,22,23,25,26*). Others have found similar decreases in cerebral metabolism in dogs (*23*) and in chronic polydrug abusing men studied with PET (*27*). The effect of the opioid antagonist naloxone, however, is less clear. Some have shown that it increases CBF in normal control animals (*15,17,20*) while causing vasodilatation of pial vessels and increases in cerebral blood volume (*16,18*). It has also been shown, in similar models, that naloxone reverses the decrease in CBF caused by morphine (*22,23*) and that it improves CBF in ischemic brain tissue (*19,21*) and neurological deficit (*13,14*). Others have found the opposite, however, that it causes decrement in CBF in normal brain; (*21,28*) that it offers no clinical (*29*) or perfusion (*30,31*) benefit, or actually impairs CBF in ischemic brain; (*13*) or that it dangerously increases cerebral metabolism in injured tissue (*32*). A single PET study in patients with complex partial epilepsy showed no change in cerebral metabolism but a decrease in CBF after an injection of naloxone (*33*).

The possible effects of a potent, mixed opioid agonist-antagonist, such as buprenorphine, are thus difficult to

predict. It is clear that buprenorphine has little of the systemic cardiovascular and respiratory effect of direct opioid agonists (*34*), and that it is a safe and effective potential treatment for drug addiction (*35*). Few studies, however, have examined the effect of buprenorphine on CBF. Stein and Fuller used autoradiography to evaluate rCBF in rats 15 min following buprenorphine administration (*36*). They found that buprenorphine increased CBF in several regions in a dose-response fashion, with a moderate dose associated with the greatest effect. Two other studies in mongrel dogs using the hydrogen clearance technique showed either a slight decrease (*37,38*) or no change (*22*) in CBF with buprenorphine administration of 10–1000 μg/kg. The authors' previous study of cocaine polydrug-dependent men showed marked improvement in rCBF in areas identified as abnormal at baseline after treatment with buprenorphine (*12*). There was also mild improvement in these abnormal areas before buprenorphine treatment was initiated, suggesting an effect of abstinence as well. Since this was a preliminary study without a placebo control group, however, direct comparison of the relative effects of abstinence and buprenorphine was difficult. In addition, in the absence of a control group, serial measurement of areas of abnormality, as previously employed, may be complicated by regression to the mean. The current study was prospectively designed specifically to avoid these potential confounders and enable a direct comparison of abstinence and buprenorphine on rCBF.

There are several limitations to this study, the foremost being the extreme difficulty in controlling potentially confounding conditions in this patient population, as well as the complex interactions that may occur during abstinence from polydrug abuse. This difficulty is highlighted by the finding that patients maintained on placebo actually had an increase in the number of perfusion defects over time. These patients were polydrug-dependent, many for a number of years, and were being maintained drug-free after a short detoxification period with methadone. Besides the fact that methadone is primarily useful for withdrawal from opiates and not cocaine, these patients (while not exhibiting the overt symptoms of acute withdrawal) were certainly in a period of acute abstinence or early protracted abstinence (*39–41*), both states being associated with specific physiological abnormalities. It is uncertain how cerebral perfusion would be affected under these complicated conditions of abstinence. If buprenorphine treatment reduces abnormalities in cerebral perfusion, it is reasonable to hypothesize that lack of treatment during early protracted abstinence would be associated with no change, or perhaps a worsening, as was observed. The dose-response relationship between buprenorphine and augmented CBF complements both rCBF findings in rats (*36*) as well as information as to the optimal efficacious dose of buprenorphine for drug addiction treatment in patients (*42*).

The ramifications of improvement of abnormal CBF by mixed opioid agonist-antagonists are many. It may help to explain the usefulness of these compounds in treatment of drug addiction and, potentially, the importance and nature of abnormalities in rCBF observed in this population. In addition, such a drug could well prove useful in other settings, such as in acute cerebrovascular disease or in conditions in which cerebrovascular circulation is chronically compromised, potentially including safer analgesia without impairment of cerebral perfusion.

CONCLUSION

SPECT was used to serially evaluate rCBF in a placebo-controlled, dose-escalating paradigm of buprenorphine treatment of chronic cocaine-polydrug-dependent men. These data indicate that buprenorphine, and not abstinence alone, can lead to an improvement in abnormal cerebral perfusion.

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