Cocaine as a Risk Factor for Neuroleptic-Induced Acute Dystonia

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Background: A prospective study was conducted to test the hypothesis that cocaine use is a risk factor for neuroleptic-induced acute dystonia (NIAD).

Method: The study sample consisted of a high-risk group for NIAD, males aged 17–45 years who had received high-potency neuroleptics within 24 hours of admission and had not used neuroleptics in the month prior to admission. Patients were excluded if they suffered from a neurodegenerative disorder or were exposed to anticholinergics, benzodiazepines, promethazine, carbamazepine, phenytoin, or levodopa during the study. Twenty-nine patients—9 cocaine users and 20 nonusers—entered the study, which lasted 2 years. Patients were followed for 7 days.

Results: Cocaine-using psychiatric patients developed significantly more NIAD than did nonusers (relative risk = 4.4, 95% CI = 1.4 to 13.9).

Conclusion: Cocaine use is a major risk factor for NIAD and should be added to the list of well-known risk factors. The authors strongly suggest that cocaine-using psychiatric patients who are started on a regimen of neuroleptics should also be administered an anticholinergic for at least 7 days to prevent NIAD.

(J Clin Psychiatry 1998;59:128–130)

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Supported by a grant to Dr. van Harten from the NASKHO (The Netherlands Antilles Foundation for Clinical Higher Education).

We thank the medical and nursing staff and patients of the Dr. D. R. Capriles Clinic for their support and enthusiasm during this study.

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Neuroleptic-induced acute dystonia (NIAD) is a common side effect that almost always occurs within 5 days in patients who have just been started on a regimen of neuroleptics or who have had their dosage substantially increased. The sudden onset and unpredictability of NIAD often cause fear and anxiety. Attacks can be very painful and occasionally are even life-threatening.[1]

The known risk factors for NIAD are male gender, younger age, neuroleptic potency and dose, and a history of NIAD.[1] Two reports, however, have suggested that cocaine might be a risk factor, too. In a laboratory study in which seven people were given cocaine and haloperidol simultaneously, six developed NIAD.[2] One retrospective study suggested that NIAD was three times more likely to occur in cocaine users than in nonusers.[3] However, the laboratory study with seven patients was small and not representative for psychiatric patients, and the retrospective nature of the second study restricted the usefulness of the results. We conducted a prospective study to test the hypothesis that cocaine is a risk factor for NIAD.

PATIENTS AND METHOD

The study was performed at the psychiatric hospital (Dr. D. R. Capriles Clinic) on the island of Curaçao, which is the only psychiatric hospital in the Netherlands Antilles. The characteristics of the inpatient population of this hospital at June 1, 1992, have been described elsewhere.[4] There are about 250 admissions per annum. The general policy followed by the acute care psychiatry inpatient service for psychotic patients was to prescribe high-potency neuroleptics, preferably without prophylactic anticholinergics.

The patients included in this study were admitted between June 1, 1993, and June 1, 1995. The study sample consisted of a high-risk group for NIAD, males aged 17–45 years who had received high-potency neuroleptics within 24 hours of admission and had not used neuroleptics in the month prior to admission. Patients were excluded if they suffered from a neurodegenerative disorder or were exposed to anticholinergics, benzodiazepines, promethazine, carbamazepine, phenytoin, or levodopa during the study. Lower potency neuroleptics were excluded to reduce the possible confounding effects of their intrinsic anticholinergic activity. Data were collected on age, DSM-III-R diagnosis, mean dose and peak dose of neuroleptics (before NIAD), other medication, and the use of cocaine and cannabis. The neuroleptic dose was converted into chlorpromazine dose equivalents (CPZe).[5]

Cocaine use was defined as the use of cocaine or base (a cocaine derivative) within 24 hours prior to admission on the basis of either (a) evidence from urinary samples or (b) a positive answer to questions about recent cocaine use during the admission interview. Urinary samples were collected within 24 hours after admission and checked for cocaine and cannabis, defined as more than 100 ng/mL for tetrahydrocannabinol-carboxylic acid and more than 300 ng/mL for benzoyl-ecgonine. The results were confirmed by chromatographic procedures.[6] The results of the urinary sample were not revealed to the attending resident doctor until the file was closed.

NIAD was defined as the sudden onset, within 7 days after the start of neuroleptic treatment, of sustained muscle contractions, which frequently caused twisting and repetitive movements or abnormal postures but resolved rapidly after the intramuscular administration of 5 mg of biperiden.[7] Nurses, who were not informed about the purpose of the study, were instructed to report NIAD. Diagnosis of dystonia was confirmed by the attending resident doctor. Since almost all cases of NIAD occur within 5 days of neuroleptic treatment, the files were closed after 7 days.[1]

Chi-square tests were used to compare categorical data, and an analysis of variance was used to compare continuous data.[8] Standard deviations were determined for all mean values.

RESULTS

During the 2-year study period, 29 patients, 20 classified as nonusers of cocaine, 9 classified as users, fulfilled the inclusion criteria and gave informed consent. The urine of 4 patients was not obtained within 24 hours. Of these, the first 2 reported cocaine use and were classified as cocaine users; the third patient denied using cocaine and was classified as a nonuser; the fourth patient was mentally retarded and was unable to give reliable information about cocaine use. He was classified as a cocaine user, because his family reported that he had used cocaine recently. Of the 9 cocaine users, 5 were diagnosed as suffering from schizophrenia, 3 from mania, and 1 from cocaine-induced psychosis. Of the 20 nonusers, 15 were diagnosed as suffering from schizophrenia and 5 from mania. Cocaine users did not differ significantly from nonusers in mean ± SD age (31.2 ± 6.2 vs. 33.9 ± 7.0 years; $F = 0.94$, $p = .66$), in mean daily dose (467 ± 146 vs. 612 ± 240 CPZe; $F = 2.77$, $p = .10$), or in mean peak neuroleptic dose (531 ± 191 vs. 756 ± 362 CPZe; $F = 3.06$, $p = .09$). Nine of the 29 patients developed NIAD. Significantly ($p = .01$, Fisher's exact test) more cocaine users developed NIAD (6 of 9) than did nonusers (3 of 20), which yielded a relative risk of 4.4 (95% CI = 1.4 to 13.9). The mean time between the start of neuroleptics and the development of NIAD was 55.1 ± 28.8 hours (range, 21–100 hours), and there was no significant difference in the rate of onset in the cocaine users and in the nonusers (54 ± 31 vs. 58 ± 30 hours; $F = 0.03$, $p = .9$). The neuroleptics used were penfluridol, clopenthixol, haloperidol, flupentixol, droperidol, fluphenazine, and pimozide, and no difference was found in the type of neuroleptic used by the NIAD group and the non-NIAD group. Twenty-six patients were Afro-Caribbean, 1 was white, and 2 were from a mixed marriage.

DISCUSSION

This prospective study shows clearly that cocaine use is a major risk factor for NIAD (relative risk = 4.4) in patients suffering from a psychosis treated with high-potency neuroleptics. The fact that cocaine is frequently used by psychiatric patients emphasizes the clinical importance of our finding.[9] To our knowledge, this is the first prospective study that has investigated the relationship between cocaine and NIAD.

This study has limitations. The urine of four patients was not sampled for cocaine metabolite, but these patients were included in the study. Two of these patients admitted cocaine use, the third denied it, and the fourth patient was classified as a cocaine user on the basis of information supplied by the family. Classification as a cocaine user on the basis of a positive answer by the patient to an interview question regarding cocaine use can be considered valid.[9] However, the classification in the third and fourth patient is doubtful, since denial of drug use among users is common, and information supplied by the family might be inaccurate or subject to revision. One could argue that results would differ if the third and fourth patients (neither developed acute dystonia) were later reclassified as a user or as a nonuser. Such reclassification would yield three outcomes, each different from the one reported in the original results. All three outcomes remain significant. The relative risk would vary between 3.8 (95% CI = 1.2 to 12.1) and 5.3 (95% CI = 1.7 to 16.1). If only the 25 patients whose urine was sampled were included in the study, the relative risk would be 4.22 (95% CI = 1.3 to 13.8).

It is unlikely that any other drug could be responsible for these results, because on the island of Curaçao drug abuse is limited almost exclusively to cocaine (or base) and cannabis. Another possibility is that a different risk factor for NIAD occurs more often in cocaine users than in nonusers. However, no difference was found between the cocaine users and nonusers with regard to the known risk factors of NIAD, such as mean age, mean neuroleptic dose, peak dose, and type of neuroleptic used.

Our findings are supported by a recent animal study showing that cocaine targets the dopamine transporter.[10] It has been suggested that NIAD is caused when the compensatory increase in dopamine release from neuroleptic

drugs overrides the dopamine receptor blockade as blood and brain levels of neuroleptic decline.[1] At that time, dopamine receptors may be transiently supersensitive in response to their blockade by the neuroleptic. When cocaine blocks the dopamine transporter, it causes a dramatic increase in the dopamine concentrations in the extracellular space.[10] Thus, it could be possible that cocaine users possess manipulated dopamine receptors that are prone to NIAD. However, this suggestion remains hypothetical, because the relationship between cocaine metabolites in the urine and the blood levels of cocaine is impossible to define reliably.

Our results strongly suggest that cocaine-using psychiatric patients who start taking neuroleptics should be provided with some protection against neuroleptic-induced acute dystonia, which the coadministration of anticholinergics will supply.[1]

Drug names: biperiden (Akineton), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), droperidol (Inapsine), fluphenazine (Prolixin and others), haloperidol (Haldol and others), levodopa (Larodopa), phenytoin (Dilantin and others), pimozide (Orap), promethazine (Phenergan and others).

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