Cardiovascular Interactions of Desipramine, Fluoxetine, and Cocaine in Cocaine-Dependent Outpatients

Richard A. Nelson, M.D., David A. Gorelick, M.D., Ph.D., Robert M. Keenan, M.D., Ph.D., Gilberto N. Carmona, B.S., Lino Covi, M.D.

The authors investigated the subacute cardiovascular effects of cocaine use alone and with antidepressants. At study entry, 55 cocaine-dependent (DSM-III-R) patients with cocaine-positive urines had slightly higher resting heart rates and blood pressures than 36 patients with cocaine-negative urines, which achieved significance ($P < 0.05$) for three of eleven parameters. A repeated-measures analysis of medication-compliant patients found no significant cardiovascular differences between cocaine-positive and cocaine-negative urine conditions for either desipramine ($n = 10$) or fluoxetine ($n = 20$). Cocaine use appears to produce minimal subacute cardiovascular effects, which are not accentuated by desipramine or fluoxetine, in physically healthy cocaine-dependent patients. (American Journal on Addictions 1996; 5:321–326)

The antidepressants desipramine, a first-generation tricyclic, and fluoxetine, a selective serotonin reuptake-inhibitor (SSRI), are widely prescribed medications used in the treatment of several psychiatric disorders, including cocaine abuse and dependence.[1–3] Both of these drugs, as well as cocaine, can produce cardiovascular effects, mediated in part by their similar actions on presynaptic neurotransmitter reuptake.[4–6] These shared pharmacologic mechanisms raise the possibility that patients on desipramine or fluoxetine may experience acute and/or long-term adverse cardiovascular consequences with concomitant cocaine use. The high comorbidity between depression and cocaine use[7] and frequent relapse to cocaine use among many patients receiving pharmacotherapy in cocaine-abuse treatment programs[8] suggests that such concomitant use is a common occurrence.

Received July 20, 1995; revised December 6, 1995; accepted December 21, 1995. From the National Institutes of Health, National Institute on Drug Abuse, Division of Intramural Research, Treatment Branch, Baltimore, MD. Address correspondence to Dr. Gorelick, NIH/NIDA-DIR Treatment Branch, P.O. Box 5180, Baltimore, MD 21224.

Two experimental studies have investigated the cardiovascular effects of acute cocaine use in human subjects taking desipramine. Fischman et al.[9] found that desipramine alone (mean serum level 134 ng/ml) increased the resting heart rate (HR) and blood pressure (BP) of six cocaine users above baseline; upon the administration of intravenous cocaine (up to 32 mg), HRs remained stable, whereas BPs acutely increased, reaching higher levels than those found for cocaine alone. In a similar study, Kosten et al.[10] also found that desipramine alone (mean serum level 173 ng/ml) produced increases in resting HR and BP in five cocaine users. Intravenous cocaine (up to 0.5 mg/kg) produced additional acute HR and BP increases; however, the absolute levels reached did not significantly differ from those found for cocaine alone.

One experimental study has addressed the effects of fluoxetine on the cardiovascular response to cocaine. In a study of five healthy cocaine users administered fluoxetine (mean serum level of fluoxetine and norfluoxetine combined: 135 ng/ml at highest fluoxetine dose) and intravenous cocaine doses of up to 40 mg, Walsh et al.[11] observed that fluoxetine may slightly increase cocaine's acute pressor effects; however, this trend was not statistically significant for any cardiovascular measure.

The subacute (1–2 days post-use) cardiovascular effects of cocaine in the outpatient setting, alone or with medication, have not been systematically examined. Characterizing these effects is important both to ascertain the long-term cardiovascular consequences of chronic cocaine use and to develop rational risk–benefit guidelines for the use of antidepressants in known or suspected cocaine users.

This report presents a retrospective analysis of data from two outpatient cocaine-abuse treatment trials to assess the subacute cardiovascular effects of recent cocaine use on cocaine-dependent patients both before and while receiving either desipramine or fluoxetine.

METHODS

Data were obtained from a retrospective chart review of two 12-week, outpatient, double-blind, placebo-controlled clinical trials to evaluate the efficacy of desipramine and fluoxetine in the treatment of cocaine dependence (DSM-III-R criteria). Patients were separately recruited for the two trials and separately randomized to receive either 1) desipramine (up to 300 mg daily) or active placebo (diphenhydramine, 50 mg daily), or 2) fluoxetine (20, 40, or 60 mg daily) or inactive placebo. All subjects were physically healthy at study intake, based on medical history, physical examination, and clinical laboratory testing, including electrocardiogram (ECG). Other current psychoactive substance dependence (except caffeine and tobacco) or serious mental illness were excluded on the basis of history and urine drug screening.

During each trial, patients reported to the NIDA-Division of Intramural Research outpatient clinic 3 days per week, where they provided urine specimens under direct staff observation (subsequently analyzed for evidence of illicit drug use), completed psychological questionnaires, reported any physical symptoms, and received the oral treatment medication. Also, patients received twice-weekly individual counseling and referrals to appropriate community substance abuse clinics for further treatment or follow-up.

At each clinic visit, after a minimum 10-minute period of sitting in the waiting area, patients also had their sitting HR and BP measurements taken by a registered nurse or trained technician (using an IVAC model #4000-AEE automatic BP monitor), and then received repeat measurements after standing for 1 minute.

Urines were screened for the presence of benzoylecgonine with the Roche Diagnostic Systems Abuscreen Radioimmunoassay, which uses antigen–antibody binding with a cutoff of 300 nanograms per

milliliter for a "cocaine-positive" result. This test has been shown experimentally to detect recent cocaine use (20 mg IV) 1–2 two days post-exposure.[12]

All medications were distributed as pills for twice-daily oral ingestion. To corroborate medication compliance, four times throughout each trial, patients had blood samples drawn that were subsequently assayed for medication level. (Fluoxetine serum levels were assayed by National Psychopharmacology Laboratory, Inc., Knoxville, TN. Desipramine levels were assayed by Citrano Medical Laboratories, Baltimore, MD.)

A total of 135 patients consented to these trials. Data from two subsets of patients were selected for analysis in this report. To assess the effects on cardiovascular parameters of recent cocaine use without medication, 91 patients with complete HR, BP, and urine toxicology data from the first study visit (before beginning treatment medication) were divided into "cocaine-positive" and "cocaine-negative" groups based on urine toxicology results from that first visit.

Data from these two groups were compared by use of a one-way, between-subjects analysis of variance (ANOVA) for each cardiovascular parameter examined. To examine the possibility of cocaine–alcohol or cocaine–gender interactions, a multivariate ANOVA was also performed, incorporating gender and alcohol use as cofactors in the analysis.

To assess the cardiovascular effects of recent cocaine use while subjects were on antidepressant medication, 47 subjects with at least 2 weeks on medication were selected who 1) had visits with one positive and one negative cocaine urine toxicology result (in no specific order) within 2 weeks of each other, 2) displayed blood levels of treatment medication indicative of medication compliance, and 3) had complete HR and BP data for both visits. A two-way mixed analysis of covariance (ANCOVA) was performed, comparing each medication group to its control group to determine the effects of medication (between-subjects), cocaine use (within-subjects), and medication–cocaine use interactions.

For both sets of analyses, the dependent variables were six directly measured cardiovascular parameters: sitting and standing HR, systolic BP (SBP) and diastolic BP (DBP), and five derived measures: sitting and standing mean arterial pressure (MAP; $(SBP + 2 \times DBP)/3$) and sitting-to-standing (standing minus sitting) changes in HR, systolic BP, and diastolic BP.

All statistical tests were performed with the SPSS statistical package for Windows, using two-tailed alpha level of 0.05 (uncorrected for multiple comparisons). To assess the sensitivity of these tests, the differences detectable with a power of 0.8 were also calculated, by use of standard methods for independent and paired samples and variances obtained in the data as estimates of the population variance.[13]

RESULTS

On demographic and self-reported drug use characteristics, the "cocaine-positive" and "cocaine-negative" patient groups differed significantly at the first visit only in the percentage reporting any cocaine use in the past 48 hours ($F_{[1, 89]} = 22.68$; $P < 0.0001$; Table 1).

On cardiovascular measures, the cocaine-positive group had significantly greater standing diastolic (81.9 mmHg vs. 75.4 mmHg, respectively; $F_{[1, 89]} = 7.27$; $P = 0.008$) and mean arterial (97.8 mmHg vs. 91.5 mmHg; $F = 5.83$; $P = 0.018$) BPs and significantly different systolic orthostatic (+2.8 mmHg vs. –2.5 mmHg; $F = 4.20$; $P = 0.043$) BP changes than the cocaine-negative group. The cocaine-positive group also had slightly greater resting HRs, sitting BPs, and orthostatic changes than the cocaine-negative group, although none of these other differences reached statistical

TABLE 1. Sociodemographic and self-reported drug use characteristics of "cocaine-positive" vs. "cocaine-negative" outpatients, mean ± SD

	Total	Positive	Negative
n	91	55	36
Age, years	30.0 ± 5.4	30.5 ± 5.6	29.3 ± 5.1
Men, %	85	86	83
White/Black, %	57/43	55/45	61/39
Cocaine use			
"Regular use," years	3.8 ± 3.2	3.4 ± 2.9	4.5 ± 3.4
Days use in past 30 days	17.0 ± 8.3	18.0 ± 8.3	15.5 ± 8.2
Any cocaine, past 48 hours, %	47.2	64.8	19.4***
Alcohol use			
"Regular use," years	3.3 ± 4.7	3.8 ± 5.2	2.4 ± 3
Days use in past 30 days	8.4 ± 8.6	8.8 ± 9.1	7.8 ± 8.0
Other illicit drugs, days use in past 30 days			
Marijuana	5.1 ± 7.8	4.4 ± 7.6	6.2 ± 8.
Heroin	0.6 ± 1.7	0.5 ± 1.5	0.8 ± 2.
All other	1.1 ± 2.4	1.5 ± 2.9	0.6 ± 1.2

Note: SD = standard deviation.
***$P < 0.001$.

significance (Table 2). For this test, the estimated differences detectable with a power of 0.8 were 7 mmHg, 10 mmHg, and 8 beats per minute (bpm) for diastolic BP, systolic BP, and HR, respectively.

A multivariate analysis of variance with self-reported alcohol use (divided into equal-sized "low-," "intermediate-," and "high-" use groups) and gender as cofactors found no significant interaction effects between urine toxicology result and either gender or self-reported alcohol use for any cardiovascular measure (not shown).

For subjects on medication, no significant differences between medication and placebo groups were found for age, gender, self-reported alcohol use, or cocaine use before study entry. Mean (± standard deviation [SD]) serum concentrations of treatment medication were 134 ± 74 ng/ml for the desipramine group and 233 ± 162 ng/ml for the fluoxetine group (fluoxetine and norfluoxetine levels combined), at the low end of the therapeutic range for both medications.[14-16]

On cardiovascular measures, for the desipramine and the active-placebo groups, no significant medication effects or cocaine–medication interactions were found. Recent cocaine use was associated only with a significantly greater increase in HR in moving from sitting to standing position (13.2 bpm

TABLE 2. Cardiovascular measures at first visit in cocaine-dependent outpatients, mean ± SE

	Positive ($n = 55$)	Negative ($n = 36$)
Sitting		
Systolic BP	126.8 ± 2.2	126.3 ± 1.9
Diastolic BP	75.2 ± 1.6	71.9 ± 1.5
MAP, mmHg	92.4 ± 1.7	90.0 ± 1.5
HR	74.5 ± 1.8	73.4 ± 1.9
Standing		
Systolic BP	129.6 ± 2.4	123.8 ± 2.9
Diastolic BP**	81.9 ± 1.7	75.4 ± 1.4
MAP*	97.8 ± 1.8	91.5 ± 1.7
HR	83.9 ± 2.0	82.2 ± 2.4
Orthostatic change (standing minus sitting)		
Systolic BP*	+2.8 ± 1.5	−2.5 ± 2.3
Diastolic BP	+6.6 ± 1.0	+3.6 ± 1.6
HR	+9.4 ± 1.2	+8.8 ± 1.3

Note: SE = standard error; BP (blood pressure) and MAP (mean arterial pressure) measures are in mmHg; HR (heart rate) measures are in bpm (beats per minute).
*$P < 0.05$; **$P < 0.01$.

vs. 2.6 bpm; $F_{[1, 16]} = 7.75$; $P = 0.013$).

Mean (± standard error [SE]) systolic BP, diastolic BP, and HR for the 10 desipramine subjects in the cocaine-positive vs. cocaine-negative condition were, respectively, 127.8 ± 3.2 mmHg vs. 126.0 ± 4.6 mmHg, 80.2 ± 3.1 mmHg vs. 78.2 ± 2.7 mmHg, and 80.1 ± 4.7 bpm vs. 86.7 ± 3.6 bpm while sitting, and 125.3 ± 4.8 mmHg vs. 122.6 ± 5.2 mmHg, 80.9 ± 3.1 mmHg vs. 76.3 ± 3.2 mmHg, and 93.3 ± 4.8 bpm vs. 89.3 ± 4.0 bpm while standing.

Similarly, for the fluoxetine and inactive-placebo groups, no significant medication effects or cocaine–medication interactions were found. As before, recent cocaine use was significantly associated only with sitting-to-standing changes in HR. However, in this instance, recent cocaine use was associated with a decreased orthostatic response (6.8 bpm vs. 12.9 bpm; $F_{[1, 26]} = 9.52$; $P = 0.005$).

Mean (± SE) systolic BP, diastolic BP, and HR for the 20 fluoxetine subjects in the cocaine-positive vs. cocaine-negative condition were, respectively, 124.2 ± 3.0 mmHg vs. 125.9 ± 3.0 mmHg, 70.0 ± 2.8 mmHg vs. 71.1 ± 2.6 mmHg and 74.0 ± 3.9 bpm vs. 68.2 ± 2.5 bpm while sitting, and 124.4 ± 2.4 mmHg vs. 123.3 ± 3.2 mmHg, 76.3 ± 2.5 mmHg vs. 76.3 ± 2.3 mmHg, and 82.1 ± 3.6 bpm vs. 81.5 ± 3.4 bpm while standing.

For these tests, the differences detectable with a power of 0.8 were calculated to be (for diastolic BP, systolic BP, and HR, respectively): 10 mmHg, 11 mmHg, and 10 bpm for the fluoxetine–placebo comparison, 14 mmHg, 20 mmHg, and 16 bpm for the desipramine–diphenhydramine comparison, and 6 mmHg, 9 mmHg, and 11 bpm for the effects of recent cocaine use (both groups).

DISCUSSION

In this sample of medically screened cocaine-dependent outpatients, a cocaine-positive urine was associated with minor increases in BP and HR, consistent with the known sympathomimetic effects of cocaine, which achieved statistical significance for only one of six directly measured and two of five derived cardiovascular parameters. Power calculations for this analysis indicate a sufficient sensitivity to detect clinically meaningful BP and HR differences. These findings suggest that in physically healthy individuals, cocaine use subacutely produces only minor cardiovascular effects with limited clinical significance.

Similarly, these results suggest that recent cocaine use does not interact with the antidepressants fluoxetine or desipramine to significantly alter cardiovascular status, except for accentuated orthostatic pulse increases in the patients taking diphenhydramine or desipramine and orthostatic pulse decreases in the patients taking placebo or fluoxetine. This interaction could be indicative of an alteration in sympathetic function produced by either cocaine or subacute cocaine withdrawal and modified by diphenhydramine and desipramine. To our knowledge, such an alteration has not been associated with an increased risk of adverse cardiovascular events.

The finding of no significant desipramine effect on HR or BP in this comparison, contrary to its known effects, is probably a reflection of the limited power of this analysis to detect medication (between-subjects) effects. By contrast, this analysis does appear to have sufficient sensitivity to detect clinically significant (within-subjects) effects from recent cocaine use, if these were present.

The failure to find, in outpatient cocaine abusers, the same additive cardiovascular effects with desipramine reported in an experimental study[9] suggests that this interaction may not be frequent or robust enough to be clinically significant in an outpatient setting and that the use of desipramine in this population may be relatively safe. Likewise, the absence of any direct or interactive cardiovascular effects of fluoxetine with cocaine in this study suggests that this antidepressant may also be relatively safe for treatment in cocaine abusers.

There are two limitations to the above conclusion: 1) acute cocaine–desipramine or cocaine–fluoxetine interactions may exist that produce greater, but shorter-lived cardiovascular effects than were assessed by this study design (in which a time interval of up to 72 hours could separate cocaine use and the subsequent measurement of cardiovascular parameters); 2) the possibility that cocaine–desipramine or cocaine–fluoxetine interactions increase the risk for cardiac arrhythmias, thought to be a major mechanism for cocaine's lethality,[17] was not addressed by this study.

To evaluate these two possibilities would require both detailed, accurate information on the amounts and timing of cocaine use and the use of continuous BP and ECG monitoring. Collection of such information from patients in the natural environment may prove challenging.

CONCLUSIONS

Although cocaine's acute cardiovascular effects have been extensively studied in experimental settings, less attention has been paid to cocaine's possible subacute effects in realistic outpatient settings. The results of this retrospective review of two treatment trials indicate that cocaine use produces only minimal subacute changes in HR and BP, either by itself or together with either desipramine or fluoxetine, in physically healthy cocaine-dependent outpatients. Although the existence of problematic acute interactions remains possible, these results suggest that, subacutely, the use of these antidepressants in physically healthy cocaine-dependent patients who may relapse to cocaine use is relatively safe.

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