Effects of nifedipine pretreatment on subjective and cardiovascular responses to intravenous cocaine in humans

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Received August 9, 1989 / Final version January 7, 1991

Abstract. The effects of oral nifedipine pretreatment on subjective and cardiovascular responses to intravenous cocaine infusions were studied in cocaine-using volunteers. Nifedipine, 10 mg or placebo, was administered 20-25 min before placebo, 20 mg, or 40 mg cocaine, using a repeated measures randomized double-blind design. The variables measured were self-reported subjective effects, general behavior rated by two observers, blood pressure and heart rate. Cocaine produced the expected dose-related effects on subjective and cardiovascular measures. Nifedipine pretreatment attenuated some subjective effects of cocaine. Nifedipine directly reduced blood pressure but did not antagonize the effects of cocaine on blood pressure. These findings suggest that dihydropyridine calcium channel modulators may be useful compounds in the clinical management of cocaine users.

Key words: Nifedipine – Cocaine – Blood pressure – Heart rate

Cocaine use has increased over the last decade (Kozel and Adams 1986) and has been associated with such cardiovascular disorders as acute myocardial infarction, cardiac arrhythmias, myocarditis, and sudden death (Cregler and Mark 1986). Studies in rats on the action of nitrendipine, a dihydropyridine calcium channel modulator, and cocaine (Nahas et al. 1985; Trouve and Nahas 1986) suggest that Ca ++ antagonists can counteract some aspects of the cardiac toxicity of cocaine by preventing the decrease of coronary blood flow and the arrhythmias induced by cocaine, as well as by protecting the heart from cocaine-induced acute morphological lesions. With six male human subjects, however, pretreatment with 60 mg diltiazem, a benzotheiazepine calcium channel antagonist, appeared to diminish cocaine-induced effects on skin temperature, but not on cardiovascular or subjective effects (Rowbotham et al. 1987). These latter results were possibly due to diltiazem’s not crossing the blood-brain barrier.

Dihydropyridine calcium channel modulators are mainly used for treating cardiovascular disease, because of their potent peripheral and coronary arterial dilator activity (Bonaduce et al. 1983; Serruys et al. 1983). Nifedipine, a widely used dihydropyridine effective in treating angina and essential hypertension (Sorkin et al. 1985), is known to cross the blood-brain barrier (Duhm et al. 1972) and might be expected to produce similar cardiovascular effects as were found with nitrendipine in rats. The purpose of the present study was to determine whether nifedipine could antagonize the cardiovascular and also possibly the subjective effects of cocaine in humans. Because nifedipine is known to cross the blood-brain barrier, the measurement of subjective effects may help to determine whether dihydropyridine calcium channel modulators may be potential therapeu tic compounds for cocaine abuse.

Materials and methods

Subjects. Ten male volunteers, 27-42 years old (mean age 34 years), participated in the study approved by the Institutional Review Board of the Francis Scott Key Medical Center; written informed consent was obtained from all subjects. Initial criteria for subject selection included a history of recent intravenous cocaine use and passage of the vocabulary part of the Shipley-Hartford Retreat Scale with a minimum mental age score of 12.3 (Shipley 1940). Criteria for subject inclusion were HIV negative status, passage of a physical examination and laboratory screening tests, including EKG. Subjects were excluded if they fulfilled criteria for current DSM III Axis I (APA 1980) disorders other than substance abuse disorders. Subjects were admitted to a closed research ward, and random urine screens were performed throughout the study period to ensure that subjects were exposed only to those substances administered as part of the research protocol. Following admission to the ward, the nursing staff observed subjects for signs and symptoms of sedative or opiate withdrawal. None of the study subjects exhibited signs of withdrawal or illicit drug use during the 3-day minimum baseline washout period.
After medical evaluation, subjects were tested for unusual sensitivity to cocaine using a series of single IV injections of cocaine, while cardiac functioning was monitored by EKG. Doses of placebo and 10, 20, and 40 mg cocaine were delivered in a pseudorandomized order under double-blind conditions, such that the 20 mg dose of cocaine was always scheduled before the 40 mg dose. A minimum of 24 h elapsed between test doses. On the basis of this preliminary testing, two research volunteers were rejected for further study due to unusual cardiovascular reactivity. One subject withdrew for personal reasons for a final sample of seven.

The psychiatric status of each participant was assessed with the National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS; Robins et al. 1980) adapted for computer administration. Two subjects had a history of major depressive disorder. Within the substance abuse disorders, five subjects had a history of alcohol dependence, five of tobacco dependence, two of barbiturate dependence, and four of opioid dependence. Finally, three subjects had a history of cannabis abuse and three of cocaine abuse. Two subjects had a history of antisocial personality disorder, three others had features of this diagnosis, and one subject had a history of pathological gambling. All subjects had been using cocaine continuously during the last 5 years. Average reported frequency of cocaine use was 8 days per month and average reported quantity of use per day was 0.64 g. The seven selected subjects had used IV cocaine within the 3 weeks prior to participating in the study. All subjects had a history of alcohol, tobacco, opioid, and cannabis use.

Procedure. Subjects remained on the ward during the safety screening and study periods for an average of 4 weeks. After successful completion of the safety screening, subjects participated in the study and received six different experimental drug conditions presented in a randomly determined order. These conditions were: (1) placebo oral pretreatment followed by placebo IV administration, (2) placebo oral pretreatment followed by 20 mg IV cocaine administration, (3) placebo oral pretreatment followed by 40 mg IV cocaine administration, (4) 10 mg nifedipine oral pretreatment followed by placebo IV administration, (5) 10 mg nifedipine oral pretreatment followed by 20 mg IV cocaine administration, and (6) 10 mg nifedipine oral pretreatment followed by 40 mg IV cocaine administration. The 10 mg nifedipine dose is the standard initial dose for treatment of cardiac problems. We had intended to extend the study to higher doses of nifedipine, but in three subjects single 20 mg doses of nifedipine produced consistently elevated heart rates prior to cocaine administration, which precluded the testing of nifedipine with cocaine.

Experimental sessions were scheduled no more frequently than every 48 h. Each session was conducted under double-blind conditions in the same sound-insulated room. A physician, and sometimes two physicians were present during the first hour of the experiment. Two research nurse/technician observers were always present throughout the study period. Observers refrained from talking with each other or initiating conversation with the subjects and provided a supportive but non-directive milieu in their interactions with the subjects. Cardiac function was continually monitored prior to and for the first 30 min after the injection, and periodically thereafter. Intervention protocols were in place to respond in the event of medical emergencies.

On each study day, following an overnight fast and a standard breakfast 2 h before the infusion, an indwelling IV heparin lock catheter was inserted into a forearm vein and flushed with heparinized saline 60 min before receiving the infusion. Subjects reclined in bed during the sessions. Oral pretreatments with nifedipine 10 mg or placebo (lactose) were administered in identical gelatin capsules 20 min before the start of the injection. Cocaine or placebo (saline) infusions were administered using a pressure pump (Sage Instruments Syringe Pump model 341) which infused drug into the indwelling catheter via a needle inserted into the heparin lock over a period of 12 s. The start of the infusion was determined by a computer which was programmed to activate the pump randomly during a 5-min interval after the attending physician pressed a start key. No visual or auditory cues indicated the moment in which the infusion started; a "beep" sounded 2 min after the end of the infusion. This randomized time of infusion meant that pretreatment and measurement times prior to the infusion varied by as much as 5 min between subjects. Subjects rested in bed during the 30 min following the infusion. Limited ambulation was allowed thereafter, but subjects were not permitted to exercise.

Measures. Subjects' blood pressure and heart rate were measured at 60 and 10 min before the infusion and 2, 10, 15, 30, 55, 85, and 115 min after the injection. Systolic and diastolic blood pressure and heart rate were sampled via a BARD Biomedical Sentinel automated blood pressure monitor. Cardiac monitors could not be seen by the subjects.

We used a computer-administered 30-item rating scale (Kumor et al. 1989; Muntaner et al. 1989) as a measure of the subjective effects produced by IV cocaine administration. The items were rated on a five point scale (1 = not at all to 5 = extremely). Principal components analyses of the 30-item scale for the present set of subjects guided the construction of six subscales with good face validity. These subscales were labeled General Drug Effect (8 items: "How confused does the drug make you feel?", "How much rush do you feel?", "How high do you feel?", "How much do you feel the drug?", "How strong do you feel?", "How weird do you feel?", "How much do you feel the drug?", "How high do you feel?", "How anxious does the drug make you feel?"); Feel Good (5 items: "How good do you feel?", "How clear is your thinking?", "How good does the drug make you feel?", "How pleasant do you feel?", "How pleasant does the drug make you feel?"); Suspiciousness (3 items: "How suspicious do you feel?", "Can the staff tell what you are thinking?", "How uncomfortable do you feel?"); Craving (2 items: "How much do you need cocaine?", "How much do you want cocaine?"); Sexual Arousal (2 items: "How sexy do you feel?", "How powerful do you feel?"); and Crash (1 item: "How much crash do you feel?"). We also used a 10-point computer-administered bar-graph, called Rushgraph, to measure the euphoric subjective effect sometimes termed "rush" (Kumor et al. 1989; Sherer et al. 1989). The scales were administered at 60 and 10 min before the beginning of the injection and at 2, 10, 15, 30, 55, 85, 115 min after the injection.

A computer-administered form of the Profile of Mood States (POMS; McNair et al. 1971) consisted of 65 adjectives commonly used to describe transient mood states. The POMS includes six scales (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment), with between 7 and 15 items comprising each scale. The POMS was administered at 60 min before the injection and at 15, 60, 90, and 120 min after the injection.

Two observers rated the subjects using the Single Dose Questionnaire for Observers (Haertzen 1974), which has been used in studies of opiate effects. The Single Dose Questionnaire is a checklist that includes items of behaviors commonly observed after opiate administration. Observers rated subjects on 1) any evidence of drug effect, 2) the degree to which the behavior observed was like that seen after cocaine, 3) 14 behavioral/mood items, and 4) the subjects' liking for the drug. Preliminary analyses showed that no changes were observed across drug conditions on most items. Three items did provide consistent variation across conditions: "Is the behavior observed like that seen after cocaine?", "high", and "liking for the drug." These three variables were analyzed separately.

A second rating scale, the Observer's Cocaine Rating Scale, was designed for the recording of behaviors specifically observed after cocaine administration. This instrument consists of 18 items (available from the authors by request). Preliminary analyses showed little variability on ten items. The remaining eight items ("clammy hands and feet", "restless", "happy/euphoric", "perspiration", "unable to concentrate", "dry mouth", "energetic," and "tremulous/shaky hands") were summed to form a single scale. Items were rated on a 3-point rating scale (0 = none, 1 = somewhat, 2 = a lot). All observers had experience in the observation of cocaine-induced behaviors. In keeping with procedures used for many years at the ARC for observer ratings of opioid effects, subjects' spontaneous comments were used in rating drug effects but were not