Nifedipine Protects the Heart From the Acute Deleterious Effects of Cocaine If Administered Before but Not After Cocaine

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Background. We tested the hypothesis that nifedipine, a calcium channel blocker, could ameliorate the toxic effects of cocaine on the myocardium.

Methods and Results. In an initial protocol, anesthetized dogs were pretreated with nifedipine or saline and then administered cocaine (10 mg/kg, i.v. bolus). Coronary blood flow, heart rate, mean arterial pressure, and the first derivation of left ventricular pressure (dP/dt) were measured at baseline, 2 minutes, and 15 minutes after cocaine administration. Nifedipine pretreatment prevented the early cocaine-induced decrease in coronary blood flow and improved left ventricular dP/dt compared with untreated control animals. After cocaine, ejection fraction fell in the saline group to 37 ± 3% but increased in the nifedipine group to 59 ± 4% (p < 0.05). In a second protocol, vehicle or intravenous nifedipine was administered after an infusion of cocaine (10 mg/kg). In contrast to pretreatment, there was no significant improvement in left ventricular function or coronary blood flow in nifedipine-treated versus control animals. Data from the study also suggested that cocaine acts directly on the myocardium. Within seconds of cocaine bolus administration, coronary blood flow in control animals increased to a peak level 59 ± 14% higher than before cocaine and left ventricular dP/dt decreased by 23 ± 5%, providing evidence that cocaine causes direct depression of myocardial function independent of a decrease in myocardial blood flow.

Conclusions. We conclude that nifedipine administered as a pretreatment protects against the depression of myocardial function and decrease in coronary blood flow caused by acute cocaine administration. However, when nifedipine is given after cocaine, no improvement is seen. Cocaine has a direct negative inotropic effect on the heart that is independent of a decrease in coronary blood flow. (Circulation 1991;83:1437–1443)

The adverse effects of cocaine on the heart have been documented both clinically and experimentally. Numerous reports have associated cocaine use with ventricular arrhythmias, myocardial infarction, and sudden death. Experimentally, cocaine administration has been shown to cause constriction of coronary arteries both in vitro and in vivo. It reduces myocardial blood flow, and cause significant depression in left ventricular function. Whether the depression in function is a consequence of the decrease in blood flow due to constriction of coronary arteries or is a direct action of cocaine on the heart is unknown. The first hypothesis of this study was that the decrease in left ventricular function may be a consequence of the decrease in blood flow to the heart due to constriction of major coronary arteries by cocaine.

It has been shown that calcium channel blockers can prevent or reverse coronary artery vasoconstriction, and these agents have been especially effective as a therapy for Prinzmetal’s angina. Rongione et al have reported that nifedipine inhibits cocaine-induced constriction in isolated rabbit aortic rings. Our hypothesis was that nifedipine could prevent contraction of coronary arteries in an in vivo model, thus preventing the decrease in blood flow and improving left ventricular function after cocaine administration. We studied the effects of nifedipine in two protocols. To test the effects of calcium channel blockade before cocaine, nifedipine was given as a pretreatment and
then cocaine was administered. Then nifedipine was given after the administration of cocaine to mimic a more clinically relevant scenario.

**Methods**

**Animal Preparation**

Mongrel dogs weighing 16–43 kg were anesthetized with sodium pentobarbital (35 mg/kg i.v. bolus for induction and then as needed to ensure adequate depth of anesthesia), intubated, and the lungs were ventilated. Cannulae were inserted into the left jugular vein to administer fluids and into the left carotid artery to monitor systemic blood pressure. Lead II of the electrocardiogram was monitored and recorded. Left thoracotomy was performed and the pericardium excised. To measure end-diastolic pressure and the first derivative of left ventricular pressure (dP/dt), a Millar (Houston, Tex.) microtipped pressure transducer was inserted into the left ventricle by way of the left atrial appendage. A Transonics Doppler flow probe was placed around an isolated section of the circumflex coronary artery for continuous measurement of coronary blood flow. An insertion sheath was placed in the right femoral artery, and the animals were given 150 units/kg heparin.

**Experimental Protocol 1: Pretreatment With Nifedipine**

After a 10-minute period of stabilization, animals were randomized by lot to one of two groups: either pretreatment with nifedipine (10 mg) or control. The nifedipine was removed from a capsule with a needle and syringe and administered sublingually. Fifteen minutes was allowed for onset of action of the drug, then coronary angiography was performed by an injection of 6–8 ml of nonionic contrast medium (Omnipaque). Measurement of hemodynamics and coronary artery blood flow were obtained. Cocaine (10 mg/kg) was then injected as an intravenous bolus for 30 seconds. Hemodynamic and coronary angiographic measurements were taken again 2 and 15 minutes after cocaine administration. Left ventriculography was performed before randomization and after the final coronary arteriogram, 15 minutes after cocaine administration, to measure stroke volume and left ventricular ejection fraction. At the end of the experiment, the dogs were killed under anesthesia by an intracardiac injection of potassium chloride (40–60 meq).

**Protocol 2: Treatment With Nifedipine Subsequent to Cocaine Administration**

After stabilization, hemodynamic measurements were obtained and angiography and ventriculography were performed. To allow time for the onset of action of the nifedipine, dogs in this second protocol were administered cocaine (10 mg/kg) by intravenous infusion for 10 minutes. All measurements were repeated, and then animals were randomized to control or nifedipine treatment. Nifedipine (5 μg/kg) was given by intravenous infusion for 3 minutes. Chosen based on previous work in our laboratory, this dose causes a modest decrease in systemic pressure but does not affect left ventricular dP/dt. An intravenous preparation of nifedipine was made by dissolving 5 mg nifedipine in 15 ml polypropylene glycol and 15 ml ethanol. After dissolution, the solution was diluted to 100 ml with distilled water. Control animals received the same solution without nifedipine (vehicle). At 15 and 30 minutes after nifedipine or control treatment (30 and 45 minutes after the start of the cocaine infusion), all measurements were repeated.

**Fluoroscopic Measurements**

Arteriography and ventriculography were performed using a Seimens (Iselin, N.J.) Cardoskop-U, and cines were recorded on a Siemens Sirecord-E. Views of the heart were obtained in the anterior/posterior projection, with the dog on its right side. Arteriography was performed by an injection of 6–8 ml of nonionic contrast medium (Omnipaque), and ventriculography was performed by injection of 25 ml Hypaque at a rate of 12 ml/sec. Circumflex artery diameter was measured by projecting the arteriogram and tracing the circumflex artery at diastole. The caliber was measured at three points along the length of the artery, and the three measurements were averaged. Left ventricular area and chord length was measured at both systole and diastole by projecting, tracing, and then quantifying the ventriculogram image by planimetry with a Summasketch digitizing pad (Summagraphics Corp., Seymour, Conn.) and SigmaScan software (Jandel Scientific, Corte Madera, Calif.). Left ventricular volume at systole and diastole, stroke volume, and ejection fraction were computed. All tracings were done by a person blinded to the treatment of the dog at the time the tracing and planimetry were performed.

**Statistical Analyses**

**Protocol 1.** To compare changes in variables before and after nifedipine and control pretreatment, data were analyzed by Student’s t test for group data. To compare differences in the two groups at baseline, 2 minutes, and 15 minutes after cocaine administration, two-way analysis of variance for group and time effects was used (SAS, Cary, N.C.).

**Protocol 2.** To compare changes after cocaine infusion with baseline values in the same animals, data were analyzed by t test for paired data. To compare differences in the two groups after cocaine (but before nifedipine or vehicle) and at 15 minutes and 30 minutes after nifedipine or vehicle administration, data were evaluated using two-way analysis of variance. When the F ratio exceeded the critical value p<0.05, contrasts were used for comparisons of means. All values are expressed as mean±SEM.

**Results**

A total of 47 dogs were in the study. Of the 31 dogs in protocol 1, one animal died before the administration of cocaine. Of the remaining dogs, 17 were randomized to the control group and 13 to the
nifedipine group. Six control dogs and two that received nifedipine died within 5 minutes of cocaine administration. These animals were eliminated from the study. Thus, data for protocol 1 are reported on the surviving 11 control and 11 nifedipine-treated animals. Sixteen dogs entered protocol 2. Data from one dog were excluded because of pulsus alternans at baseline, and one dog randomized to control died before completing the protocol. Data are given for seven control and seven treated animals.

Protocol 1

Effect of pretreatment with nifedipine. As expected, treatment with nifedipine caused a reduction in mean arterial pressure compared with the control condition. Mean arterial pressure in nifedipine-treated animals was 80±4 mm Hg and in control animals was 113±6 mm Hg (p<0.001) versus control). All other parameters measured were similar in both groups before cocaine administration.

Effects of bolus of intravenous cocaine on hemodynamics in control (n=11) and nifedipine-treated (n=11) groups (Table 1). Heart rate was significantly reduced in both groups 2 minutes after cocaine administration and remained below baseline at 15 minutes. Mean arterial pressure was reduced in control animals from 113±6 to 68±10 mm Hg (p<0.001) 2 minutes after cocaine but at 15 minutes had returned to baseline. In animals pretreated with nifedipine, mean arterial pressure did not change after cocaine administration. End-diastolic pressure was elevated in both groups 2 minutes after cocaine. End-diastolic pressure returned to baseline at 15 minutes in the nifedipine-treated group but remained slightly but significantly elevated in the control group.

Cocaine administration reduced coronary artery blood flow (Table 2) in the control group by 61%, from 46±6 ml/min to 18±5 ml/min (p<0.0001) at 2 minutes, and at 15 minutes blood flow was still reduced compared with baseline. However, pretreatment with nifedipine completely prevented the early cocaine-induced decrease in coronary artery blood flow. In nifedipine-treated animals, coronary blood flow was 42±7 ml/min before cocaine and was 41±6 ml/min and 36±4 ml/min at two and 15 minutes after.

Cocaine caused a small, nonsignificant reduction in mean circumflex coronary artery diameter in both control and nifedipine-treated groups (Table 2).

Effect of nifedipine or vehicle on cocaine-induced left ventricular dysfunction (Table 3). Left ventricular stroke volume and ejection fraction were calculated from left ventriculograms obtained before cocaine (before randomization) and at 15 minutes after cocaine injection (Table 3). Cocaine caused a decrease in both stroke volume and ejection fraction in control animals. However, in nifedipine-treated animals, stroke volume and ejection fraction were significantly higher than in control animals.
TABLE 3. Protocol 1: Ventriculogram Data

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>15 minutes after cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>27±2</td>
<td>22±3</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>28±4</td>
<td>37±4*</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>50±3</td>
<td>37±3</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>55±5</td>
<td>59±4*</td>
</tr>
</tbody>
</table>

*p<0.001 vs. control.

Nifedipine afforded partial protection against the decrease in left ventricular contractility caused by cocaine. Before cocaine administration, values for left ventricular dP/dt were similar in both groups (2,105±117 mm Hg/sec for control and 2,239±121 mm Hg/sec for nifedipine-treated). Left ventricular dP/dt (Figure 1) was reduced in control animals by 60% to 849±166 mm Hg/sec at 2 minutes after injection of cocaine. In contrast, dP/dt in nifedipine-treated animals was significantly higher than in the control group, 1,341±104 mm Hg/sec after cocaine (p<0.0001 versus control). At 15 minutes, both groups were similar; however, dP/dt did not return to baseline in either group.

Protocol 2

Effect of cocaine infusion (before treatment with nifedipine or vehicle, n=14). Cocaine infusion had an adverse effect on hemodynamics in all animals in protocol 2. End-diastolic pressure was elevated from 5±0 to 10±1 mm Hg (p<0.0001). Heart rate was reduced from 145±4 to 124±3 bpm (p<0.0001). Mean arterial pressure was unchanged (112±4 versus 114±5 mm Hg). Coronary blood flow was reduced from 28±3 to 23±2 ml/min (p<0.005), and there was a small but significant reduction in circumflex artery diameter from 2.5±0.1 to 2.2±0.1 mm (p<0.005). The infusion of cocaine caused a deterioration in left ventricular function. Ejection fraction decreased from a baseline value of 53±4% to 36±3% (p<0.002). Stroke volume decreased from 25±2 to 20±2 ml (p<0.04). Left ventricular dP/dt was similarly depressed, falling from 2,322±124 to 1,555±99 mm Hg/sec (p<0.001).

Ventricular dimensions were also altered by the infusion. End-diastolic volume increased from 49±5 to 55±5 ml (p<0.05), and end-systolic volume increased from 25±4 to 36±4 ml (p<0.001). These data suggest that cocaine caused an acute dilation of the left ventricle.

Effect of nifedipine treatment when administered after cocaine infusion (n=7 for control and n=7 for nifedipine-treated animals). Five μg/kg nifedipine given after cocaine failed to improve hemodynamics compared with the control group (Table 4). Coronary artery blood flow was similar in both groups, as was circumflex artery diameter (Table 5). Although ejection fraction and stroke volume were above baseline values in the nifedipine-treated group and below baseline in the control group at 30 minutes after treatment (45 minutes after nifedipine), there were no significant differences between groups (Table 6).

Additional Observations

Data obtained immediately after intravenous injection of cocaine provide evidence that cocaine has a direct negative effect on left ventricular function that is independent of a decrease in myocardial blood flow.
flow. In control animals, coronary artery blood flow increased within 30 seconds of injection, reaching a mean peak level 59±14% higher than the mean baseline value. Concomitant with the increase in blood flow, left ventricular dP/dt decreased by 23±5% (Figure 2); then blood flow decreased. This phenomenon was also observed in nifedipine-treated animals but to a lesser extent. Blood flow increased to a peak level 39±5% higher than baseline, and dP/dt decreased by 12±5%.

**Discussion**

Data from this study indicate that pretreatment with nifedipine, a calcium channel blocker, can ameliorate the acute cardiodepressive effects of cocaine. In untreated animals, cocaine caused a significant decrease in left ventricular ejection fraction and stroke volume and reduced myocardial contractility; pretreatment with nifedipine prevented this. In nifedipine-treated dogs, stroke volume and ejection fraction were not depressed by cocaine, and myocardial contractility was preserved to a greater extent than in control animals.

Cocaine injection caused only a small reduction in epicardial coronary artery diameter in both groups 2 minutes after administration. However, in the control group coronary artery blood flow fell by 61%. It is possible that the reduction in coronary blood flow was a consequence of the reduction in diastolic pressure and thus oxygen demand or reduced coronary perfusion pressure; it was not due to a direct effect of the cocaine on the caliber of large coronary arteries. However, diastolic pressure was reduced by nifedipine treatment per se, but coronary flow remained similar to that of the control group until cocaine was given. In nifedipine-treated animals blood flow did not change, suggesting that the protective effect of pretreatment with nifedipine was not due to its action on large epicardial coronary arteries. Vitullo et al. reported that infusion of cocaine in isolated rat hearts induced spasm in coronary arteries, and larger caliber vessels did not constrict. This spasm was reversed by nitrendipine.

Other studies have shown calcium channel blockers to be efficacious in the treatment of cocaine-induced myocardial toxic effects. Trouve and Nahas were the first to suggest calcium channel blockers as an antidote to cardiac toxic effects of cocaine. Their study showed that nitrendipine increased survival time and tolerated dose in rats and also prevented the acute morphological lesions that they observed after cocaine administration. Nitrendipine was selected because of its dilator effects on large and resistance vessels. Billman et al. showed that cocaine can induce ventricular fibrillation during ischemia. These lethal arrhythmias were prevented by the calcium channel blocker verapamil.
Vitullo et al.\textsuperscript{17} studied isolated perfused rat hearts. They observed decreases in flow and contractility in paced hearts that were attenuated by nitrendipine treatment. In our study, we chose to test nifedipine based on reports by Rongione et al.\textsuperscript{16} that calcium channel blockers, including verapamil and nifedipine, inhibit cocaine-caused contraction of large vessels.

The action of cocaine may be different on large and small arteries. Lange et al.\textsuperscript{9} have shown that in large epicardial arteries, cocaine-induced vasoconstriction is reversed by phentolamine, an $\alpha$-adrenergic blocking agent. However, Vitullo et al.\textsuperscript{17} reported that spasm in small arterioles was not prevented by phentolamine but was prevented by nitrendipine, a calcium channel blocker. However, Rongione et al.\textsuperscript{16} have shown in the rabbit aorta that $\alpha$-blockade showed no consistent effect on cocaine-induced constriction of vascular smooth muscle, but calcium channel blockers inhibited the effect. They concluded that cocaine-induced constriction of vascular smooth muscle is a result of enhancement by cocaine of calcium influx across the cell membrane. Kuhn\textsuperscript{19} showed that $\alpha$-blockade both decreased the constriction of large vessels and improved the cocaine-induced increase in coronary resistance.

Data from our study support recent observations that a high dose of cocaine has a direct negative inotropic effect on the heart that is independent of a decrease in blood flow.\textsuperscript{20} Shortly after injection of cocaine, coronary blood flow increased and myocardial contractility simultaneously decreased. Fraker et al.\textsuperscript{20} observed a decrease in left ventricular ejection fraction after cocaine in both conscious dogs, for whom coronary blood flow rose after cocaine, and in pentobarbital-sedated dogs, for whom coronary blood flow decreased after cocaine. They suggested that this negative inotropic effect of cocaine is a result of its local anesthetic effects on the myocardium.

Our data suggest that it may be necessary for calcium channel blockade to be present before cocaine in order to be effective. Cocaine potentiates the effects of norepinephrine. Because catecholamines increase calcium entry into cells, nifedipine pretreatment may act by inhibiting a catecholamine-mediated overload of calcium into the myocytes. When administered after cocaine, calcium channel blockade may be ineffective because cells may already have a calcium overload, which agents such as nifedipine cannot reverse. Mechanisms explaining the protective effects of nifedipine may also include afterload reduction or improved myocardial perfusion by dilation of vascular smooth muscle of coronary arterioles.

Our study has some limitations. The dose of cocaine used in this study (10 mg/kg) is relatively large when administered over 10 minutes. Otolaryngologists routinely use 3–4 mg/kg for intranasal anesthesia. It is difficult to estimate cocaine levels used by street users, but it probably covers a wide range. Fischman et al.\textsuperscript{21} have indicated that 16 mg was the average amount used by street users; however, in a study of cocaine-related deaths, Virmani et al.\textsuperscript{22} reported a mean plasma cocaine level of 5,300±8,100 ng/ml. Experimental studies in dogs yield these plasma levels with administration of 5–15 mg/kg. An additional limitation is the use of anesthetized animals, in which some of the effects of cocaine, both systemic and on the myocardium, may differ from
conscious animal models or humans. In conscious dogs, Wilkerson et al.\(^2\) have observed that cocaine causes elevations of both heart rate and systemic pressure, but when similar doses were given to pentobarbital-anesthetized dogs, heart rate and pressure responses were reduced. However, reduction in left ventricular function and blood flow after cocaine administration has been shown to occur in both conscious animals\(^1\) and humans.\(^9\) Finally, two different methods of cocaine administration were used. In the first protocol, cocaine was administered by bolus infusion. In the second later protocol, cocaine was given by infusion over 10 minutes to allow time for the onset of action of nifedipine. The effects of cocaine seem somewhat related to the rate of administration; for example, systemic pressure decreased when cocaine was given as a bolus but remained the same when cocaine was given by infusion for 10 minutes. In addition, the time course of changes in coronary blood flow was very rapid after bolus injection of cocaine. However, after infusion of cocaine, the rate of decrease in coronary blood flow was more gradual and less severe. Therefore, it is difficult to make direct comparisons between the two protocols. It is possible that we missed a potential positive effect by nifedipine in protocol 2 either because of timing or the dose of nifedipine used.

In summary, pretreatment with the calcium channel blocker nifedipine prevented the early cocaine-induced decrease in coronary blood flow and improved left ventricular \(dP/dt\) compared with untreated controls. However, in contrast to pretreatment, there was no significant improvement in left ventricular function or coronary blood flow when nifedipine was administered after cocaine. In addition, data from this study also suggest that a large dose of cocaine acts directly on the myocardium as a negative inotropic agent.

Acknowledgments

Animals used in this study were maintained in accordance with the guidelines prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. 85-230).

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\textbf{KEY WORDS} • nifedipine • cocaine
Nifedipine protects the heart from the acute deleterious effects of cocaine if administered before but not after cocaine.

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