JACC Vol. 20, No. 1
July 1992:90–5

Hemodynamic Effects of Intranasal Cocaine in Humans

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Intranasal cocaine, 2 to 3 mg/kg body weight, is a commonly used local anesthetic for rhinolaryngologic procedures, and many persons who abuse it ingest a similar amount. Previous studies in humans showed that this dose of cocaine causes coronary vasoconstriction, and studies in animals showed that larger amounts given intravenously diminish myocardial performance. This study assessed the hemodynamic effects of intranasal cocaine, 2 mg/kg, in humans.

In 15 patients (8 men and 7 women, aged 30 to 70 years) referred for cardiac catheterization, heart rate, systemic arterial pressure, cardiac index, pulmonary capillary wedge and pulmonary artery pressures and left ventricular pressure and its first derivative (dP/dt) were measured before and 15, 30 and 45 min after intranasal administration of saline solution (n = 5) or cocaine, 2 mg/kg (n = 10). No variable changed with saline solution. In those given cocaine, there was an increase in heart rate (17 ± 16%, mean ± SD), mean systemic arterial pressure (8 ± 7%), cardiac index (18 ± 18%) and positive and negative dP/dt (18 ± 20% and 15 ± 22%, respectively) ($p < 0.05$ for all).

Thus, intranasal cocaine in a dose similar to that used medicinally or "recreationally" does not exert a deleterious influence on intracardiac pressures and left ventricular performance.

(J Am Coll Cardiol 1992;20:90–5)

Intranasal cocaine, 2 to 3 mg/kg body weight, is often used as a local anesthetic for rhinolaryngologic procedures (1,2). Although some habitual abusers of the drug use much greater amounts, most "social" or "recreational" cocaine users ingest <250 mg (2 to 4 mg/kg) at a sitting (3,4). In patients studied during cardiac catheterization, this dose of cocaine causes coronary artery vasoconstriction and a modest decrease in coronary blood flow (5). In dogs, larger amounts of intravenous cocaine cause myocardial depression, as evidenced by a decrease in the first derivative of left ventricular pressure (dP/dt) (6,7), ejection fraction (8,9), and cardiac output (9). Some reports (10,11) have even associated chronic cocaine abuse with the development of a dilated cardiomyopathy. However, the hemodynamic effects of intranasal cocaine in humans in the amounts usually employed for medicinal or recreational purposes (2 to 3 mg/kg) are unknown. This study was performed to assess these effects.

Methods

Study patients. Fifteen patients (8 men and 7 women, aged 30 to 70 years) undergoing cardiac catheterization for the evaluation of chest pain were studied. None had used cocaine previously. The protocol was approved by the Human Subjects Review Committee of the University of Texas Southwestern Medical Center, and all patients gave written informed consent. All subjects were studied in the fasting state after premedication with 5 to 10 mg of oral diazepam. All cardioactive medications were discontinued >12 h before study.

Experimental protocol. An 8F sheath was inserted percutaneously in a femoral vein, and a 9F sheath was placed in a femoral artery. An 8F Judkins catheter was advanced to the ostium of the left coronary artery, and a single cineangiogram was performed to exclude disease of the left main coronary artery. Provided this was not present, a 7.5F flow-directed, balloon-tipped thermodilution catheter was advanced to the pulmonary capillary wedge position, and an 8F micromanometer-tipped pigtail catheter (Millar Instruments) was placed in the left ventricle. Baseline recordings of heart rate and femoral artery, pulmonary capillary wedge, pulmonary artery and left ventricular pressures were performed; the first derivative of left ventricular pressure (dP/dt) was recorded and thermodilution cardiac output was measured in triplicate. Subsequently, each patient received intranasal saline solution, 2 ml (n = 5), or a 10% cocaine hydrochloride solution, 2 mg/kg (n = 10), after which all variables again were measured 15, 30 and 45 min later. The patients were unaware of which agent was given.

A sample of blood was procured 30 min after administration of cocaine, placed in a gray-top vacutainer tube containing 0.25% sodium fluoride and transferred on ice to the

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Manuscript received October 28, 1991; revised manuscript received January 2, 1992, accepted January 18, 1992.

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0735-1097/92/$5.00

Table 1. Responses to Intranasal Saline Solution (5 patients) or Cocaine (10 patients)

	Baseline	Minutes After Administration		
		15	30	45
Heart rate (beats/min)				
Saline	70 ± 7	[illegible]	68 ± 6	67 ± 7
Cocaine	68 ± 17	[illegible]	79 ± [illegible]	79 ± [illegible]
Pressures (mm Hg)				
Mean systemic arterial				
Saline	102 ± 15	[illegible]	100 ± 12	[illegible] ± 13
Cocaine	92 ± 10	99 ± 9	98 ± 15	
Systolic arterial				
Saline	150 ± 26	146 ± 21	146 ± 16	152 ± 19
Cocaine	136 ± 16	142 ± 14	140 ± 13	144 ± 15*
Mean pulmonary artery				
Saline	20 ± 6	18 ± 6	19 ± 5	21 ± 7
Cocaine	16 ± 3	16 ± 3	16 ± 3	16 ± 3
Pulmonary capillary wedge				
Saline	12 ± 6	13 ± 6	12 ± 5	15 ± 6
Cocaine	8 ± 3	8 ± 3	8 ± 3	8 ± 3
LV end-diastolic				
Saline	18 ± 8	17 ± 5	18 ± 7	20 ± 6
Cocaine	15 ± 4	15 ± 5	15 ± 4	17 ± 4
Cardiac index (liters/min per m^2)				
Saline	2.65 ± 0.41	2.6 ± 0.41	2.61 ± 0.31	2.56 ± 0.32
Cocaine	2.82 ± 0.54	2.86 ± 0.6	3.06 ± 0.76	3.31 ± 0.82*
Stroke volume index (ml/m^2)				
Saline	38 ± 8	38 ± 8	38 ± 6	39 ± 8
Cocaine	42 ± 9	40 ± 8	41 ± 8	43 ± 10
Positive LV dP/dt (mm Hg/s)				
Saline	1,427 ± 267	1,386 ± 305	1,407 ± 265	1,377 ± 305
Cocaine	1,331 ± 268	1,412 ± 278	1,461 ± 302	1,558 ± 346*
Negative LV dP/dt (mm Hg/s)				
Saline	1,707 ± 303	1,720 ± 209	1,702 ± 177	1,706 ± 206
Cocaine	1,649 ± 359	1,731 ± 361	1,778 ± 470	1,867 ± 455*
Total systemic vascular resistance (dynes-s-cm^{-5})				
Saline	1,667 ± 405	1,724 ± 439	1,670 ± 327	1,711 ± 310
Cocaine	1,363 ± 235	1,455 ± 310	1,376 ± 330	1,289 ± 327
Pulmonary vascular resistance (dynes-s-cm^{-5})				
Saline	122 ± 44	88 ± 37	115 ± 39	108 ± 36
Cocaine	143 ± 62	141 ± 59	124 ± 52	121 ± 38

*$p < 0.05$ in comparison with baseline. All data are expressed as mean value ± 1 SD. dP/dt = first derivative of left ventricular pressure; LV = left ventricular.

laboratory for immediate gas chromatographic analysis of cocaine concentration.

Statistical methods. All results are reported as mean value ± SD. Results in the two groups were compared with Student's *t* test. Within each group, the changes induced by saline solution or cocaine were assessed with a repeated measures analysis of variance. For all analyses, a p value < 0.05 was considered significant.

Results

At the time of coronary arteriography, seven patients had angiographically normal or minimally diseased coronary arteries (<70% lumen diameter narrowing); three had one-vessel coronary artery disease, four had two-vessel disease and one patient had three-vessel disease. The left ventricular ejection fraction averaged 0.64 ± 0.11 (range 0.46 to 0.83).

Intranasal saline solution (n = 5). In these patients, saline solution induced no change in any variable at 15, 30 or 45 min (Table 1).

Intranasal cocaine (n = 10). In these patients, the blood cocaine concentration 30 min after drug administration was 0.21 ± 0.08 (range 0.05 to 0.3) mg/liter. At 45 min after drug administration, heart rate, mean arterial pressure, cardiac index and left ventricular dP/dt (positive and negative) increased ($p < 0.05$) with respect to baseline (Table 1). Pulmonary artery, pulmonary capillary wedge and left ventricular end-diastolic pressures and total systemic and pulmonary vascular resistance were unchanged.

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Discussion

Previous assessments of the short- and long-term hemodynamic effects of cocaine. In studies (12) of isolated myocardial tissue from animals, cocaine at low concentrations exerts a positive inotropic effect, whereas at higher concentrations it has a negative inotropic effect and decouples excitation-contraction. In intact animals, large amounts of intravenous cocaine diminish left ventricular performance, as reflected by a decrease in positive dP/dt (6,7), ejection fraction (8,9) and cardiac output (9) as well as an increase in left ventricular volumes (7). Although cocaine has been shown to cause coronary artery vasoconstriction in animals (7) and humans (5), its depression of left ventricular performance appears to be a direct toxic effect rather than a manifestation of cocaine-induced myocardial ischemia (8).

In isolated case reports, the repetitive or long-term use of cocaine in humans has been associated with 1) acute reversible cardiac dysfunction (10), 2) a dilated cardiomyopathy (11), and 3) asymptomatic left ventricular dysfunction (13). This cocaine-induced depression of myocardial contractility has been attributed to the drug's direct toxic effect or the high concentrations of circulating catecholamines that accompany exposure to cocaine, or both (10). In contrast to these observations, a recent echocardiographic study (14) of long-term cocaine users demonstrated left ventricular hypertrophy without segmental wall motion abnormalities or chamber dilation. In short, the acute hemodynamic effects of intranasal cocaine in humans are poorly characterized. The present study was performed to examine these effects.

Comparison with previous studies. Intranasal cocaine, 2 to 3 mg/kg, is commonly employed as a local anesthetic for rhinolaryngologic procedures (1,2), and many social or recreational users ingest a similar amount (3,4). Our data demonstrate that this dose of cocaine caused a modest increase in heart rate (17 ± 16%), mean arterial pressure (8 ± 7%), cardiac index (18 ± 18%) and left ventricular positive and negative dP/dt (18 ± 20% and 15 ± 20%, respectively) ($p < 0.05$ for all). There was no change in pulmonary capillary wedge, pulmonary artery and left ventricular end-diastolic pressures or in systemic and pulmonary vascular resistance. Thus, in contrast to studies in animals showing that cocaine is a myocardial depressant, our data in humans demonstrate that cocaine is a myocardial stimulant, exerting positive chronotropic and inotropic effects.

Several factors may explain the difference between our results in humans and those obtained in animals. First, our dose of cocaine (2 mg/kg) was lower than that used in the animal studies (4 to 12 mg/kg). Second, we administered cocaine intranasally, whereas it was given intravenously in the animal studies (6–9). Previous studies (15) have shown that only 80% of cocaine is absorbed after its intranasal administration. As a result of this difference in route of administration and dosage, the peak blood concentration of drug after an intranasal dose of 2 mg/kg is 15 to 40 times lower than that achieved after an intravenous dose of 4 to 12 mg/kg (average serum cocaine concentration 0.21 mg/liter in our patients versus 3.5 (9), 4.1 (8) and 7.5 (6) mg/liter in dogs after intravenous cocaine). It is possible that very large doses of cocaine, irrespective of the route of administration, would cause an increase of intracardiac pressures and a deterioration of cardiac output and left ventricular performance. As noted, previous in vitro studies (12) suggested that the cardiac effects of cocaine are dose dependent, with lower concentrations stimulating and higher concentrations depressing cardiac performance. Although such large doses are occasionally taken by chronic abusers of the drug, studies in human volunteers with intravenous doses comparable to those used in the animal studies are not feasible.

Third, many of the animal studies were performed in anesthetized, open chest dogs. General anesthesia may minimize or negate the hemodynamic effects of cocaine by exerting a direct depressant effect on cardiac performance or diminishing the magnitude of the cocaine-induced release of catecholamines. Thus, Fraker et al. (8) and Wilkerson (16) showed that cocaine caused an increase in heart rate and mean systemic arterial pressure in conscious but not in anesthetized animals. Similarly, Catravas et al. (17) reported that the administration of large doses (0.5 mg/kg until death) of intravenous cocaine to conscious dogs caused an increase in heart rate, systemic arterial pressure and cardiac output.

Clinical implications. Intranasal cocaine (2 mg/kg) in humans causes a modest increase in heart rate, mean systemic arterial pressure, cardiac index and left ventricular positive and negative dP/dt. In no patient did this amount of drug induce a deterioration in any hemodynamic variable. Our study did not examine the immediate or long-term effects of cocaine in chronic users. Although it is possible that repetitive exposure to much larger amounts of cocaine, such as those employed by habitual users, may exert a deleterious influence, the amount used for local anesthesia and by most recreational users causes no adverse hemodynamic effects.

We acknowledge the technical assistance of Randy Christian, Nancy Smith, Kelly Sloan, Sheila Brady, Jacqui Jones, Karen Scherger and Robyn Etzel.

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