PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 183, 392-397 (1986)

RAPID COMMUNICATION

NITRENDIPINE: AN ANTIDOTE TO CARDIAC AND LETHAL TOXICITY OF COCAINE

RENAUD TROUVE AND GABRIEL NAHAS

College of Physicians and Surgeons, Columbia University, New York, N.Y., 10032 and Laboratoire de Toxicologie Cellulaire, INSERM U26, Hopital Fernand Widal, Paris 10e

Abstract. Nitrendipine, a Ca^{2+} modulator was tested in the rat as an antagonist to the cardiac toxicity of cocaine and as an antidote to the acute lethal effects of this drug. In a first series of experiments, nitrendipine (1.46×10^{-3} mg/kg/min) when simultaneously administered intraarterially with cocaine (2 mg/kg/min) suppresses the arrhythmias induced by cocaine and increases survival time from 73 ± 33 min to 309 ± 118 min and the lethal dose of cocaine from 146 ± 66 mg/kg to 618 ± 236 mg/kg ($p < 0.003$). Nitrendipine also protects the heart from the acute morphological lesions induced by cocaine administration and antagonizes some of the central effects of cocaine. In a second series, 5 rats administered 60 mg/kg of cocaine intraperitoneally had a survival time of 8'06 ± 5'20 . Death was attributed to convulsions and respiratory arrest. Animals treated with nitrendipine (129 ± 23 mg/kg) 4'30" after cocaine administration survived. Nitrendipine appears to have general protective effects against cocaine cardiac toxicity and the acute lethal effects of this alkaloid.

Introduction. While Ca^{2+} modulators have been widely used in the treatment of cardiac ischemia and coronary insufficiency (1) their use has not been suggested as an antidote to the cardiac toxic effects which may be produced by cocaine. This drug is a potent topical vasoconstrictor which inhibits the reuptake of noradrenaline and may be considered an "indirectly acting sympathomimetic amine" (2-4). The sympathomimetic properties of cocaine lead to elevations in heart rate and blood pressure in man (5) and this drug has also been reported to be cardio-toxic (6). Self-administration of cocaine is associated with dysrhythmia including ventricular fibrillation and myocardial infarction in healthy young adults (7-13) and also with stroke and intra-cranial hemorrhage (14-17). The use of propranolol which was suggested (18) to treat cardiovascular toxicity resulting from cocaine intoxication appears to have limited efficacy (19). The selection of Ca^{2+} modulators as antidotes to the sympathomimetic effects of cocaine was predicated on their known properties to inhibit the vasoconstrictive effects of norepinephrine (20-21). Nitrendipine, a dihydropyridine, was selected among the different Ca^{2+} modulators available because of its lack of depressive effect on the myocardium (22,23), at the dosage used in the present experiment, and because of its marked coronary vasodilator effect (20).

The purpose of this study was two fold. First to test the antagonistic effect of nitrendipine on the cardiac anomalies induced by acute cocaine administration; second, to test nitrendipine as an antidote to a single lethal dose of cocaine.

0037-9727/86 $1.50

Methods. Twenty fasting Sprague Dawley rats weighing 292 ± 31 g are fitted, under ether anesthesia, with catheters in the caudal artery. The catheter is connected to a constant micro-infusion pump and to a recorder for on-line recording of arterial blood pressure which is analysed and processed by a microcomputer. Measurements of heart rate and pulse pressure are displayed every 30 seconds. When the animal has awakened, it is placed in a restraining grid. The system permits continuous monitoring of vital signs in the awake animal, and rapid intervention for antidote administration, when severe failure occurs. The same caudal artery catheter is used for monitoring and administration of test substances which limits the surgical trauma to the animal. Furthermore, test substances are administered in a retrograde fashion into a distal artery often at a slow rate. The bulk of these substances is transported to the femoral artery and from there, into the venous vascular bed and the vena cava. Two series of experiments are performed. In the first series, five rats are administered a cocaine solution at the rate of 2 mg/kg/min up to a lethal dose while five others are given the same amount of cocaine concurrently with nitrendipine 1.46 μg/kg/min. After death of the animal, the hearts are removed, examined, and fixed in Bouin solution. Histological examinations are performed on horizontal sections after paraffin inclusions.

In a second series, five rats are administered 60 mg/kg of cocaine solution, intraperitoneally, a lethal dose. Five other animals are given the same amount of cocaine, followed by nitrendipine 4 to 5 minutes after cocaine administration. Nitrendipine is given intraarterially first in a loading dose of 7.4 μg, followed by a constant infusion of 1.22 μg/kg/min lasting 85 ± 20'. The end point of the perfusion was reached when the rat was becoming active and restless.

Nitrendipine was administered in a solvent provided by the manufacturer for experimental studies: it is a mixture of water, 20% polyethylene glycol 450 and glycerin. The total volume of fluid administered to the preparation was 10 μl/min and only 1/10 of this volume was diluent.

Results. First series (Table I). In 5 control animals, arrhythmias are frequent and sustained. Mean arterial pressure and heart rate tend to increase but the changes are not statistically significant. Marked agitation, tremors and convulsions are observed. Death occurs after 73 ± 33 min, following administration of a dose of cocaine of 146 ± 66 mg/kg which may be considered lethal for the rat when administered at that rate. When nitrendipine 1.46 x 10^{-3} mg/kg/min is concurrently administered with the same dose of cocaine (2 mg/kg/min), survival time is significantly increased to 309 ± 118 min ($p < 0.003$) and so is the lethal dose of cocaine (618 ± 236 mg/kg).

TABLE I: Antagonistic effects of nitrendipine on the acute toxicity of cocaine in drugs administered through the caudal artery

	Lethal dose (mg)	Survival time (min)
Cocaine (2 mg/kg/min)	146 ± 66	73 ± 33
Cocaine (2 mg/kg/min) + Nitrendipine (1.46 x 10^{-3} mg/kg/min)	618 ± 236*	309 ± 118

* $p < 0.003$

TABLE II: Effects of cocaine administration (60 mg/kg I.P.) on blood pressure and heart rate of the rat. No animals survived (Mean survival time 8'06 ± 5'20)

		minutes after cocaine administration							
TIME	CONTROL	2	4[a]	6[b]	8[b]	10[b]	12[b]	14[c]	15[c]
Mean pressure (mm Hg)	94 ±13	100 ±12	89 ±9	94 ±6	100 ± 1	107 ±10	96 ±4	97	21[e]
Heart rate (min)	418 ±26	392 ±46	371[d] ±23	365[d] ±35	370 ±40	374 ±39	443 ±75	372	242[e]

[a] Measurement on 4 surviving animals
[b] Measurement on 3 surviving animals
[c] Measurement on 1 surviving animal
[d] $p < 0.05$
[e] $p < 0.005$

Heart rate and blood pressure remain stable throughout (Table I). Throughout the experiment, the animals remain quiet and neither convulsions nor tremors are observed. Hearts from animals treated with cocaine display a vascular congestion, most apparent on the periphery, and disseminated areas of sarcolemma disruption with liberation of disorganized myocardial fibers. These morphological changes were described in a separate publication (24).

Second series: (Table II) The 5 control animals administered 60 mg/kg of cocaine intraperitoneally, had a survival time of 8'06 ± 5'20. Death could be attributed to convulsions and respiratory arrest. The heart did not present any gross morphological changes. The 5 animals treated with nitrendipine loading dose of 7.4 μg/kg followed by a constant infusion of 1.22 μg/kg/min, survived (Table III). Treatment lasted 85' ± 20' and total dose of nitrendipine administered was 129 ± 23 mg/kg. The animals were replaced, fully conscious, in their cage and 24 hours later were active and feeding themselves.

TABLE III: Effects of nitrendipine administered 5 min following a lethal dose of cocaine (60 mg/kg I.P.) on blood pressure and heart rate of the rat. All animals survived

		minutes after cocaine administration						
TIME	CONTROL	4	30	60	90	120	150	180
Mean pressure (mm Hg)	102 ±18	94 ±8	103 ±13	105 ±17	100 ± 9	110 ±11	112 ± 6	113 ±26
Heart rate (min)	416 ±26	372* ±23	392 ±46	371 ±23	365 ±35	370 ±40	374 ±39	443 ±75
		Nitrendipine						

* $p < 0.05$

Discussion This study illustrates the protective effects of nitrendipine on the cardiotoxicity of cocaine and also indicates that nitrendipine is an antidote to the lethal toxicity of cocaine. Other investigators (19) have reported that pre-treatment of dogs with chlorpromazine, pancuronium, diazepam, protected the animals against lethal doses of cocaine i.v. administered. Propranolol and pimozide were without effects. These authors also reported that hypothermia was an effective method to prevent cocaine induced lethality and concluded that hyperthermia was the most important contributor to cocaine death in dogs.

In other studies, Antelman et al. (25) observed that amitriptyline administered to rats 10 days to 24 hours before an intraperitoneal dose of 35 mg/kg of cocaine (LD_{50}) was associated with survival of the animals. Mechanisms of action of such protective effects are not clear. The potential cardiac toxicity of the large dose of cocaine administered was not reported by either group.

Yet, this "indirectly acting sympathomimetic amine" mimics some of the effects of norepinephrine which vasoconstricts human and dog coronary arteries (21,26). Administration of large doses of catecholamines will also induce myocardial and coronary lesions in the canine heart (27,28) similar to those observed in the present studies. In dogs, noradrenaline induced vasoconstriction is inhibited by calcium entry modulators (29); in the human, coronary artery contraction is antagonized by the Ca^{2+} modulator, diltiazem (30). Ca^{2+} modulators also protect the heart against the lesion induced by catecholamines (31).

In the first series of experiments, nitrendipine proved to be an effective antagonist to the acute toxic cardiac effects of cocaine. This dihydropyridine prevented appearance of arrhythmias observed in the untreated cocaine intoxicated animals. In the latter, these tachyarrhythmias consisted of extrasystoles associated with tachycardia and followed by a brief period of asystole. This Ca^{2+} modulator also prevented the appearance of cardiac morphologic alterations associated with cocaine administration as reported elsewhere (24). It would appear that cardiac toxicity of cocaine may be mostly related to an overstimulation of the adrenergic system (32). This protective cardiac action of nitrendipine against the effects of an indirectly acting sympathomimetic is in keeping with the cardio-vascular protective effects of the Ca^{2+} modulators which have been extensively described (1,31). Nitrendipine also appears to antagonize some of the effects of cocaine on the central nervous system since the animals administered nitrendipine did not convulse and remained quiet throughout several hours of cocaine perfusion. This central effect of nitrendipine was specially manifest in the second series of experiments. In these experiments, nitrendipine proved to be an effective antidote following a single lethal dose of cocaine. Survival of the animal could not only be attributed to the cardio-protective effect of the Ca^{2+} modulator but also to its stabilizing effect on the central nervous system. Convulsions and respiratory arrest were observed among the animals which succumbed in the second series without presenting arrhythmias or cardiac morphological lesions.

Nitrendipine appears to have general protective effects against the toxic effects of cocaine on the cardiac as well as the cerebral vascular bed.

Acknowledgments. The professional expertise of Dr. Colette Latour and the technical assistance of Jean Francois Demus and Maryvonne Sitbon are acknowledged with thanks.

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Received June 19, 1986.
P.S.E.B.M. 1986, Vol. 183.
Accepted October 2, 1986.