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Comparison of cocaine and Na^+ channel blockers on cardio-respiratory function in the rabbit

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Abstract

The cardio-respiratory effects of cocaine were compared to various Na^+ channel blocking Class I antiarrhythmics. Anesthetized rabbits were treated with various doses of either cocaine, quinidine, procainamide, lidocaine or flecainide. Cocaine produced clear decreases in blood pressure and heart rate. None of the other sodium channel blockers produced any change in blood pressure, and heart rate was decreased only slightly by procainamide and lidocaine. Cocaine produced larger increases in QRS duration than were observed for the four sodium channel blockers. All five drugs produced comparable increases in respiratory rate. Separate rabbits were pretreated with either the alpha-adrenoceptor antagonist phentolamine or the beta-adrenoceptor antagonist propranolol prior to cocaine. Phentolamine attenuated the blood pressure decrease following cocaine and propranolol attenuated the heart rate decrease following cocaine. These results suggest that the sodium channel blocking properties contribute only minimally to the overall effects of cocaine on blood pressure and heart rate. Further, the large effect of cocaine on QRS duration suggests that cocaine may act at sodium channels in a manner different from the other drugs. This unique effect of cocaine may contribute to the sudden death associated with cocaine use in some individuals.

Keywords: Cocaine; Lidocaine; Flecainide; Heart rate; Blood pressure; ECG

1. Introduction

Cocaine has two prominent pharmacological effects, blockade of monoamine uptake and local anesthesia (Na^+ channel blockade). Previous work has documented the importance of monoamine uptake blockade in the cardiovascular effects of cocaine. Cocaine appears to produce its sympathomimetic effects (heart rate and blood pressure increases) through this mechanism. Changes in blood pressure and heart rate occur at relatively low doses in conscious animals (0.1–1.0 mg/kg, cf. Schindler, 1996). These sympathomimetic effects of cocaine are not mimicked by local anesthetics (Fischman and Schuster, 1983; Fischman et al., 1983). In contrast, the cardiovascular effects of the sodium channel blocking properties of cocaine have not received as much attention. Cocaine does block sodium channels in cardiac tissue (Crumb and Clarkson, 1990), and at higher doses (3.0 mg/kg and greater) cocaine produces depressant effects on cardiovascular function which may well be a result of blockade of sodium channels (Schindler, 1996). These effects are usually most evident in anesthetized animals, as anesthetized animals can tolerate the higher cocaine doses. For example, at high doses cocaine produces a clear widening of the QRS, an effect that is reversed by sodium bicarbonate administration (Erzouki et al., 1993; Winecoff et al., 1994), supporting the hypothesis that this effect is mediated via sodium channels.

Other sodium channel blocking agents also have profound effects on the cardiovascular system, and sodium channel blockers are used extensively in the treatment of cardiac arrhythmias (Bigger and Hoffman, 1990). However, like cocaine (Billman, 1995; Gantenberg and Hageman, 1992), some sodium channel blockers used as antiarrhythmics can also be proarrhythmic under certain circumstances. For example, the class I_C antiarrhythmics, such as flecainide and encainide, can be proarrhythmic and produce sudden death in a subset of the population (Bigger

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and Hoffman, 1990). These differing effects of the sodium channel blockers most likely result from differences in their binding properties at sodium channels. While most of the local anesthetics produce a use-dependent block of sodium channels, this effect can range from minimal to marked depending on the agent (Hondeghem and Katzung, 1977, 1984). Class I_B agents, such as lidocaine, bind primarily to the inactivated state of the sodium channel and have fast on/off kinetics. As such, they have minimal effects on the QRS. Class I_A agents, such as quinidine, bind primarily to the activated state of the sodium channel and have intermediate on/off kinetics. Finally, class I_C agents, such as flecainide, bind preferentially to activated sodium channels (Anno and Hondeghem, 1990), have much slower on/off kinetics than the other agents (Anno and Hondeghem, 1990), and thus have larger effects on the QRS. Cocaine binds with high affinity to both the activated and inactivated state of the sodium channel and has slow on/off kinetics (Crumb and Clarkson, 1990). This similarity between cocaine and flecainide in on/off kinetics has led some authors to suggest that cocaine functions similarly to the class I_C antiarrhythmics (Bauman et al., 1994). Thus, the proarrhythmic effects of cocaine may be due to its interaction with sodium channels in a manner similar to flecainide.

The purpose of the current study was to compare the cardiovascular effects of cocaine with those of representative sodium channel blockers. The sodium channel blockers were chosen to represent each of the three class I antiarrhythmics (Bigger and Hoffman, 1990): Class I_A, quinidine and procainamide; Class I_B, lidocaine; and Class I_C, flecainide.

2. Methods

2.1. Animals and procedure

Studies were conducted in anesthetized adult rabbits, of both sexes, which ranged in weight from 2.5 to 3.5 kg. They were anesthetized with sodium pentobarbital (30–35 mg/kg, IV). A longitudinal incision was made in the neck region overlying the trachea and the trachea was exposed, cannulated and connected to a respiratory monitor (Micro-Span 9090-A, Biochem). Animals were allowed to breathe spontaneously. Respiratory activity was monitored for respiratory rate, partial pressure of CO_2 (expired, end-tidal CO_2) and percentage of arterial blood saturated with oxygen. Body temperature was maintained between 37.0 and 38.0°C (rectal) by an electric heating pad.

The carotid artery was cannulated using polyethylene tubing (PE 160) and filled with heparinized saline (10 USP units/ml). This arterial catheter was connected to a blood pressure transducer (T42-20, Coulbourn Instruments, Lehigh Valley, PA). The transducer was connected to an associated amplifier (S72-25, Coulbourn) and blood pressure processor (S77-34, Coulbourn). The blood pressure processor analyzed the raw transducer signal, giving analog outputs of systolic (SP), diastolic (DP) and mean pressure (DP + [(SP − DP)/3]) after each cardiac cycle. A computer (Apple IIe or Macintosh SE with MacLab®) measured time between cycles with a resolution of 1 ms and read the analog signals for pressure with a resolution of 1 mm Hg. These values were summed and averaged over periods of 5–30 s for subsequent analysis. Lead II of a surface EKG (speed 100 mm/s) was routinely monitored and heart rate was calculated from the EKG tracing. The jugular vein was also cannulated for intravenous (IV) administration of drug. Drug administration typically occurred 20–40 min following surgery.

All animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and all procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the NIDA/IRP and the Guide for the Care and Use of Laboratory Animals (Council, 1996).

2.2. Drugs

The drugs used were cocaine hydrochloride (NIDA Baltimore), quinidine sulfate (Sigma, St. Louis), pro-

Table 1
Baseline values prior to treatment with sodium channel blockers

Drug	Dose (mg/kg)	*N*	MBP	HR	QRS	Resp. rate
Cocaine	0.1	3	88.3 ± 2.3	283.3 ± 12.0	31.7 ± 1.7	27.7 ± 2.6
	0.3	6	78.5 ± 12.9	245.0 ± 19.8	30.0 ± 1.8	35.0 ± 3.3
	2.0	6	85.7 ± 8.1	245.0 ± 25.8	33.3 ± 2.1	36.3 ± 2.7
Quinidine	0.7	6	113.2 ± 8.0	308.7 ± 10.6	31.7 ± 2.1	31.0 ± 3.4
	4.6	6	101.3 ± 7.1	275.8 ± 6.6	29.1 ± 2.4	30.7 ± 2.5
Procainamide	0.4	3	97.6 ± 5.8	299.6 ± 14.2	34.0 ± 2.5	27.2 ± 1.6
	1.6	6	98.8 ± 5.6	281.3 ± 5.9	30.8 ± 2.0	29.3 ± 5.0
Lidocaine	0.4	3	88.3 ± 2.2	265.0 ± 6.5	28.3 ± 4.4	20.0 ± 0.6
	1.6	6	89.7 ± 0.7	264.5 ± 14.5	32.5 ± 2.5	27.0 ± 3.6
Flecainide	2.8	6	113.3 ± 6.2	287.5 ± 15.0	27.5 ± 2.1	34.8 ± 5.5
	5.6	6	113.8 ± 5.6	298.2 ± 14.6	30.8 ± 2.4	41.7 ± 4.8

cainamide hydrochloride (Sigma), lidocaine hydrochloride (Sigma), flecainide acetate (Sigma), propranolol hydrochloride (RBI, Natick MA), phentolamine mesylate (RBI). All drugs were dissolved in saline. All doses are expressed as the salt. Doses of the sodium channel blocking agents were chosen to be at least equimolar to the highest dose of cocaine tested (2.0 mg/kg).

2.3. Data analysis

Baseline values for all measures were taken 10, 5 and 2.5 min prior to drug administration. Data was also collected every min following drug administration for the first 5 min, and then every 5 min until 60 min following drug administration. The data presented is for peak effects,

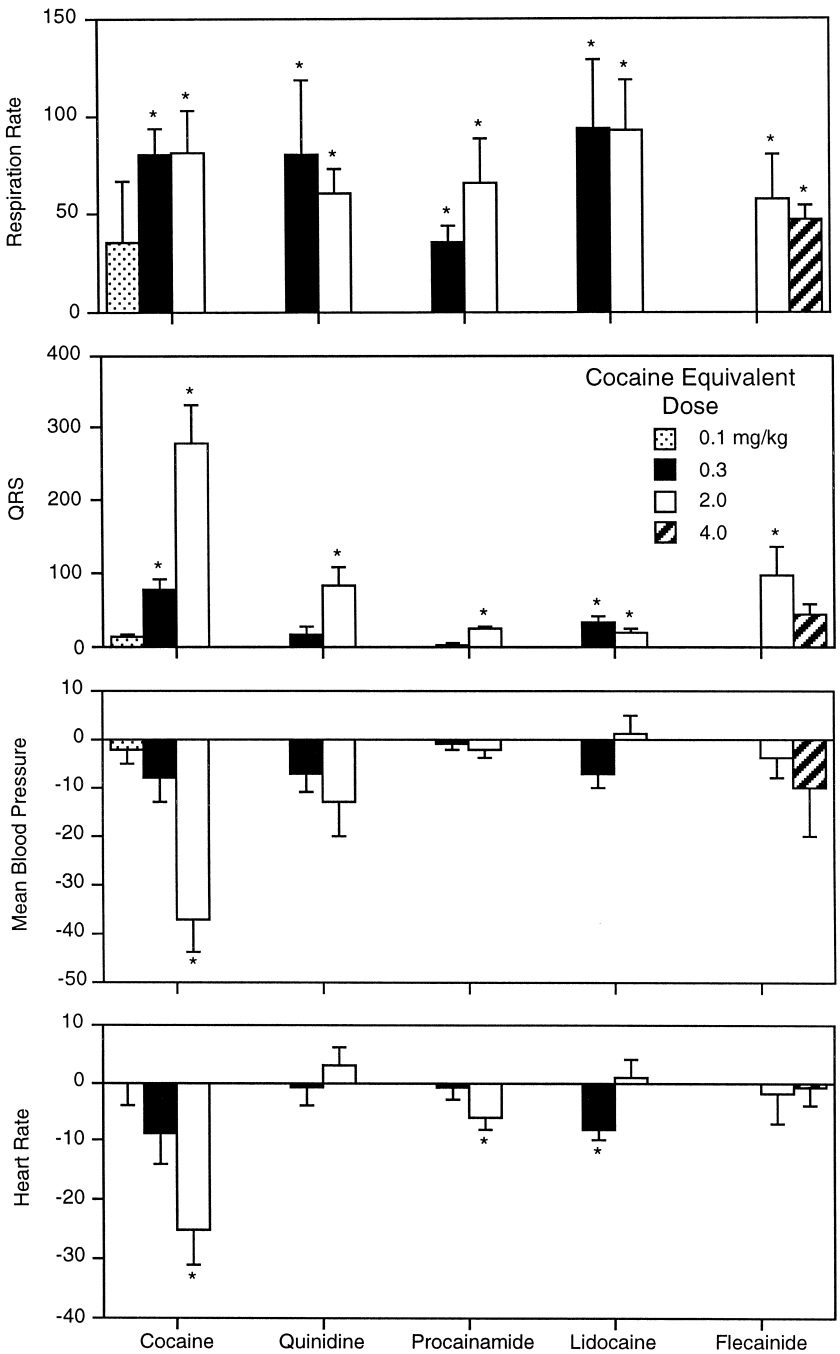

Fig. 1. Effects of cocaine, quinidine, procainamide, lidocaine and flecainide on respiration rate, QRS duration, mean blood pressure and heart rate. Measures presented are the percent change score from baseline. Dose are molar equivalent to cocaine doses. See Table 1 for actual doses and number of subjects per dose.

which were typically observed within 5 min of drug administration. Data for each compound were compared to baseline for that compound by a paired *t*-test. An ANOVA was used for comparisons across groups, with follow-up comparisons done using Fisher's LSD test (Wilkinson, 1992).

3. Results

Each rabbit was tested with only one drug and at only one dose. Baseline values did not differ systematically across groups and are shown in Table 1. Fig. 1 shows the percent change in respiration rate, QRS duration, mean blood pressure and heart rate following administration of 0.1, 0.3 and 2.0 mg/kg cocaine. Cocaine produced significant increases in respiration rate and QRS duration at the two highest doses tested. At the 2.0 mg/kg dose, blood pressure and heart rate were also decreased. The other four drugs were tested at doses that were equimolar to the 2.0 mg/kg cocaine dose and a dose either below or above that dose. The actual doses are shown in Table 1.

For respiration rate, all four sodium channel blockers produced effects that were comparable to cocaine. However, for the other measures, the effects of the sodium channel blockers were considerably different from that of cocaine. All four sodium channel blockers produced significant increases in QRS duration, but the effect of cocaine was much larger. While flecainide doubled the QRS duration, the effect of cocaine was to increase the QRS duration almost 4 fold. Procainamide and lidocaine had even smaller effects than flecainide. None of the sodium channel blockers produced a change in blood pressure, while cocaine clearly decreased blood pressure. Heart rate was decreased slightly by procainamide and lidocaine, but again, the effect of cocaine was nearly three times larger.

To investigate further the pharmacological mechanisms for the cocaine effect, separate groups of animals were pretreated with the alpha-adrenoceptor antagonist phentolamine (0.3 mg/kg) or the beta-adrenoceptor antagonist propranolol (0.15 mg/kg). These doses were chosen based on previous work (Schindler et al., 1992) and preliminary data to produce effects specific to alpha and beta adrenoceptors. The results are shown in Table 2. Animals treated with cocaine alone or pretreated with propranolol showed significant decreases in blood pressure, while those animals pretreated with phentolamine did not. Likewise, animals treated with cocaine alone or pretreated with phentolamine showed significant decreases in heart rate, while those animals pretreated with propranolol did not. Neither propranolol nor phentolamine altered the effect of cocaine to increase QRS duration, and while all three groups also showed increases in respiration rate, the effect was significantly reduced in phentolamine treated animals.

4. Discussion

The effects of cocaine on blood pressure and heart rate were similar to those reported previously in anesthetized rabbits (Rhee et al., 1990; Gardin et al., 1994). At high doses, both blood pressure and heart rate were reduced. We have observed similar effects in our laboratory with anesthetized rats (Erzouki et al., 1993).

Unlike cocaine, none of the other sodium channel blockers effected blood pressure, and heart rate was only slightly reduced by procainamide and lidocaine. The beta-adrenoceptor antagonist propranolol attenuated the heart rate effect of cocaine, while the alpha-adrenoceptor antagonist phentolamine attenuated the blood pressure effect. These findings together suggest that the depressant effect of cocaine on blood pressure and heart rate is not due to its effects on sodium channels, as previously suggested (Schindler, 1996). Rather, these depressant effects of cocaine, which are most evident in anesthetized animals, may be mediated via adrenoceptors. Most likely, this interaction occurs in the central nervous system, where norepinephrine can have inhibitory as well as excitatory effects at a number of different sites (McCall, 1990). In fact, other investigators have reported that cocaine can produce sympathetic inhibition through actions in the central nervous system (Raczkowski et al., 1991), and that these actions can be inhibited by both phentolamine (Hernandez et al., 1996) and propranolol (Gillis et al., 1993).

Cocaine as well as the other sodium channel blockers produced increases in respiratory rate. The mechanism for this effect is not clear. While the similarity between all the drugs may suggest that sodium channel blockade is involved, the fact that phentolamine partially attenuated this effect in cocaine-treated animals also suggests involvement of adrenoceptors in the effect of cocaine. In fact, many of the sodium channel blockers have effects on other receptor

Table 2
Effects of cocaine alone and in combination with phentolamine and propranolol on cardiovascular function and respiration, $n = 4$ per group

Drug treatment	% Change in MBP	% Change in HR	% Change in QRS	% Change in resp. rate
Cocaine 2.0 mg/kg	$-39 \pm 7^{*}$	$-32 \pm 7^{*}$	$277 \pm 81^{*}$	$83 \pm 16^{*}$
Phentolamine + cocaine	-20 ± 7	$-23 \pm 4^{*}$	$190 \pm 39^{*}$	$25 \pm 6^{*\dagger}$
Propranolol + cocaine	$-33 \pm 9^{*}$	-17 ± 11	$233 \pm 66^{*}$	$56 \pm 10^{*}$

$^{*}p < .05$ from baseline.
$^{\dagger}p < .05$ from cocaine alone.

systems (Bigger and Hoffman, 1990), so involvement of other receptor systems in the effects of the other sodium channel blockers cannot be ruled out.

The effect of cocaine most often attributed to sodium channel blockade is QRS widening. Indeed, cocaine produced significant QRS widening in the current study, as did all the other sodium channel blockers. This is in line with previous work in other species, including rats (Hale et al., 1989; Erzouki et al., 1993), and dogs (Schwartz et al., 1989). However, cocaine produced QRS widening which was clearly greater than the other channel blockers. Because of the manner in which they interact with sodium channels, class I_B agents would not be expected to produce much widening of the QRS. In fact, lidocaine produced only minimal changes in the QRS. However, class I_C agents would be expected to produce large changes in the QRS. Flecainide did increase the QRS duration by almost two fold at a dose equivalent to 2.0 mg/kg cocaine, but this effect was still much smaller than the over three fold increase in the QRS duration produced by cocaine. Doubling the flecainide dose produced no further increase in QRS duration. This suggests that cocaine is more efficacious than the other sodium channel blockers in widening the QRS, and may interact with the sodium channel in a unique way. While cocaine and flecainide both have slow on/off kinetics, cocaine binds with high affinity to both the activated and inactivated sodium channels, whereas flecainide has highest affinity at the activated channel. These differences in the mode of action of cocaine and flecainide may account for the differences in the efficacies of the compounds in widening the QRS.

As a result of its high affinity for both the activated and inactivated states of the sodium channel and its slow unbinding properties, cocaine most likely alters normal cardiac conduction in a manner sufficient to produce arrhythmias in certain individuals. The genesis of these arrhythmias may be similar to those observed with the use of other potent sodium channel blockers such as flecainide (Bigger and Hoffman, 1990), but the results of the current study would suggest that cocaine has even more potent effects on conduction. Further support for the hypothesis that cocaine induced arrhythmias are due to potent sodium channel blockade comes from studies showing that sodium bicarbonate can reverse the electrophysiological actions of cocaine (Beckman et al., 1991). Nevertheless, we cannot rule out the possibility that the pro-arrhythmic effects of cocaine are due to its sympathomimetic actions.

In summary, cocaine decreased heart rate and blood pressure of anesthetized rabbits through actions mediated at least partially by adrenoceptors. Cocaine also increased respiratory rate through an action also mediated at least partially by adrenoceptors. Cocaine produced increases in QRS duration that were much larger than those observed with other sodium channel blockers. This finding indicates that the action of cocaine at sodium channels may be unique to cocaine. In line with this observation, Winecoff et al. (1994) showed that the mechanism of action for lidocaine was sufficiently different from cocaine, that lidocaine could antagonize the effect of cocaine on QRS duration. The profound effects observed with cocaine may lead to an even greater incidence of sudden death than that observed with proarrhythmic sodium channels blockers such as flecainide.

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