Hemodynamic and Electrophysiological Actions of Cocaine
Effects of Sodium Bicarbonate as an Antidote in Dogs

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Background. Cocaine abuse has been implicated as a cause of death due to sudden cardiac arrest.

Methods and Results. We examined the hemodynamic and electrophysiological effects of cocaine administered as a series of 5-mg/kg i.v. boluses coupled with a continuous infusion in anesthetized dogs. Sodium bicarbonate (50 meq i.v.) was administered as a potential antidote in 11 of 15 dogs, and intravenous 5% dextrose was given in the remaining four. In a dose-dependent fashion, cocaine significantly decreased blood pressure, coronary blood flow, and cardiac output; increased PR, QRS, QT, and QTc intervals and sinus cycle length; and increased ventricular effective refractory period and dispersion of ventricular refractoriness. No afterdepolarizations were noted in the monophasic action potential recording. Nonsustained monomorphic ventricular tachycardia occurred spontaneously in two dogs, and sustained ventricular tachycardia could be induced by programmed stimulation at the end of the dosing protocol in five of 11 animals. Sodium bicarbonate promptly decreased cocaine-induced QRS prolongation to nearly that measured at baseline but had no effect on the other electrocardiographic or hemodynamic variables. In one dog, sodium bicarbonate administration was associated with reversion of ventricular tachycardia to sinus rhythm.

Conclusions. We conclude that high-dose cocaine possesses negative inotropic and potent type I electrophysiological effects. Sodium bicarbonate selectively reversed cocaine-induced QRS prolongation and may be a useful treatment of ventricular arrhythmias associated with slowed ventricular conduction in the setting of cocaine overdose. (Circulation 1991;83:1799–1807)

The abuse of cocaine has become a major medicsociological problem in the United States. Estimates suggest that at least 30 million Americans have tried cocaine, and more than 5 million use it on a regular basis.1,2 In addition to its other detrimental effects, cocaine usage is associated with a variety of adverse cardiovascular events, including acute myocardial infarction, arrhythmias, and death due to sudden cardiac arrest.3–9 The temporal relation between cocaine ingestion, acute myocardial infarction, and death is well established3,4; however, ventricular arrhythmias and sudden death have been described in the absence of acute myocardial infarction, suggesting that mechanisms other than ischemia may also be involved.5–9 Available data in experimental animals suggest that cocaine has both direct sodium channel-blocking10,11 and indirect catecholamine-mediated12–14 electrophysiological properties that can precipitate malignant ventricular arrhythmias. The purpose of this study was to investigate the hemodynamic, electrocardiographic, and electrophysiological effects of cocaine at high doses and to evaluate sodium bicarbonate administered intravenously as a potential antidote to the cardiovascular effects of cocaine.

Methods
Animal Preparation

Eleven adult mongrel dogs (weighing 18–26 kg) were anesthetized with 30 mg/kg sodium pentobarbital i.v. Additional pentobarbital was given as needed to maintain anesthesia. The dogs were ventilated with a Harvard respirator (Harvard Apparatus, South Natick, Mass.) connected to an endotracheal tube. Oxygen was administered through the

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Experimental Procedures

Leads II and aVL of the surface electrocardiogram were continuously monitored. All electrocardiographic intervals were determined by averaging five consecutive complexes. Baseline arterial blood gases were analyzed before cocaine administration to confirm that they were within the normal physiological range. Arterial and pulmonary artery blood gases were analyzed by an automated blood gas analyzer. Cardiac output was calculated by the estimated Fick method. Total coronary vascular resistance was calculated as mean arterial pressure divided by mean coronary blood flow and was expressed in millimeters of mercury \( \cdot \) minute/milliliter.

Ten bipolar platinum wire plunge electrodes were placed randomly throughout the left and right ventricular endocardium. Ventricular effective refractory periods were determined at each of the 10 electrode sites by the extrastimulus technique with a programmable stimulator (5325, Medtronic, Minneapolis, Minn.). A train of eight paced beats \( (S_1) \) was initiated at a cycle length of 300 msec. After the last paced beat, a premature stimulus \( (S_2) \) was delivered at a coupling interval of 250 msec. The interval between \( S_1 \) and \( S_2 \) was shortened by 5-msec decrements until \( S_2 \) failed to produce ventricular capture. The \( S_2 \)-\( S_3 \) interval was increased by 10 msec and then decreased by 1-msec steps until \( S_2 \) failed to produce ventricular capture twice. The refractory period at each site was defined as the longest interval between \( S_1 \) and \( S_2 \) that failed to produce ventricular capture. Temporal dispersion of the refractory periods as measured from the 10 electrode sites in each dog was assessed by two methods: 1) a ratio of sample variance before and after cocaine administration \( (F \text{ ratio}) \) and 2) the difference between the longest and shortest refractory period in a given dog divided by the mean refractory period in that dog and expressed as percent dispersion. The percent dispersion before and after cocaine administration was then compared.

Programmed ventricular stimulation to assess inducibility of ventricular arrhythmias was performed from one ventricular endocardial site. One extrastimulus was introduced after a train of eight ventricular-paced complexes at a cycle length of 300 msec as described above. The first extrastimulus was then positioned 10 msec beyond its refractory period, and a second extrastimulus \( (S_3) \) was introduced at an \( S_2-S_3 \) coupling interval of 300 msec. The \( S_2-S_3 \) interval was decreased by 10-msec steps until \( S_3 \) failed to produce ventricular capture. Burst ventricular pacing was performed by pacing the ventricle for 10–15 complexes. The cycle length was decreased by 10-msec steps from a cycle length of 400 msec to 250 msec. Pacing was performed twice at each cycle length.

A suction electrode was placed on the epicardial surface of the left ventricle to record monophasic action potentials. The monophasic action potential duration was measured at 90% amplitude. Filters were set between 0.5 and 500 Hz for surface electrocardiograms, between 30 and 500 Hz for bipolar intracardiac electrograms, and between 0.5 and 500 Hz for monophasic action potentials. Surface electrocardiograms, bipolar intracardiac electrograms, monophasic action potentials, arterial blood pressure, coronary artery blood flow, and pulmonary artery pressure were continuously monitored and intermittently recorded at a paper speed of 100 mm/sec with multichannel amplifiers and recorder (Electronics for Medicine, Kingwood, Tex.).

Experimental Protocol

After all baseline hemodynamic and electrophysiological data had been collected, a bolus of 5 mg/kg i.v. cocaine HCl was administered during a 5-minute period. Immediately after bolus administration, a cocaine infusion of 0.2 mg/kg/min was begun, and the infusion was continued for the duration of the study. Five minutes after completion of the first bolus, all hemodynamic and electrophysiological data were recorded, and arterial and pulmonary artery blood samples were obtained. Repeated determinations of ventricular effective refractory periods from the 10 endocardial sites were made during a 30- to 45-minute period. A second bolus of 5 mg/kg cocaine was then administered, and all hemodynamic, electrocardiographic, and blood gas data were obtained immediately before and 5 minutes after administration. Programmed ventricular stimulation was performed as described above. After programmed stimulation, a third bolus of 5 mg/kg cocaine was administered unless the second bolus had caused ventricular arrhythmia or cardiogenic shock (defined as a mean arterial pressure <60 mm Hg). Electrocardiographic and hemodynamic data were recorded immediately before and 5 minutes after the third bolus. Arterial blood was obtained for analysis of cocaine serum concentrations at baseline (before the first bolus) and during cocaine infusion immediately before and 5 minutes after each subsequent bolus. Cocaine serum concentrations were analyzed by use of gas-liquid chromatography according to the method of Javaid et al.

Sodium bicarbonate (50 meq i.v.) in 50 ml water (approximately 2 meq/kg) was administered in the 1–2 minutes immediately after data were recorded following administration of the final cocaine bolus. Hemodynamic and electrocardiographic data were recorded, and blood samples for determining arterial
blood gases and serum cocaine concentrations were drawn 5 minutes after administration of sodium bicarbonate. Programmed stimulation was repeated after sodium bicarbonate administration in nine of 11 dogs.

An additional four dogs, serving as controls, were anesthetized and ventilated as described above. Leads II and aVL were continuously monitored. Cocaine was administered in a fashion identical to that in the first 11 dogs. After the third cocaine bolus, 50 ml 5% dextrose i.v. was given instead of sodium bicarbonate. Sinus cycle length, PR, QRS, QT, QTc, and JTc were measured (Figure 1). This protocol was approved by the Animal Care Committee of the University of Illinois at Chicago and was performed according to the guidelines of the American Physiological Society.

Statistical Analysis

A one-way analysis of variance for repeated measures was used to analyze the hemodynamic, arterial blood gas, and electrocardiographic data. Student-Newman-Keuls test was used to determine where significant differences existed between means during baseline and cocaine administration. A paired Student's t test was used to compare mean ventricular effective refractory periods and mean percent dispersion of refractoriness before and after cocaine administration. An F test was also used to compare dispersion of the refractory periods before and after administration of the first cocaine bolus. The F test was performed after calculating the F ratio, which was defined as the sum of standard deviations of values obtained after cocaine administration squared divided by the sum of standard deviations of values obtained at baseline squared. An unpaired Student's t test was used to compare the effects of sodium bicarbonate and 5% dextrose on QRS duration. Differences in arrhythmia occurrence before and after bicarbonate administration were assessed with Fisher's exact test. Differences with p values less than 0.05 were considered significant. All data were expressed as mean±SD.

Results

Effects of Cocaine on Hemodynamics

The hemodynamic effects of cocaine are summarized in Table 1. Cocaine caused dose-related changes in most of the measured hemodynamic parameters. Mean arterial blood pressure decreased from 103±23 at baseline to 87±24 mm Hg immediately before the second bolus (p<0.0001). Subsequent cocaine boluses further decreased arterial pressure. Cocaine decreased mean cardiac output from 4.24±1.29 at baseline to 3.03±0.89 l/min before the second bolus (p<0.0001). The second cocaine bolus further decreased mean cardiac output to 1.98±0.59 l/min (p<0.0001). Systemic vascular resistance tended to increase after cocaine administration, but these changes were not significantly different from baseline. Mean pulmonary artery pressure did not change significantly after cocaine administration; however, pulmonary vascular resistance increased from 136±64 at baseline to 220±86 dyne·sec/cm² after the first bolus (p<0.0001).

Mean coronary blood flow decreased significantly from 16.6±14.1 at baseline to 9.6±7.2 ml/min after the first cocaine bolus (p<0.0001). Subsequent cocaine boluses further reduced coronary blood flow. Cocaine increased coronary vascular resistance from 8.6±2.9 at baseline to 17.7±10.5 mm Hg·min/ml after the second cocaine bolus (p<0.0001).

Effects of Cocaine on Electrophysiology

The first cocaine bolus significantly increased mean sinus cycle length; PR, QT, QTc, JT, and JTc

FIGURE 1. Schematic of the protocol. Continuous cocaine infusion was administered during both limbs of the protocol. *Three dogs did not receive a third bolus: two dogs had cardiogenic shock and one had ventricular tachycardia and could not be resuscitated. Two of these three dogs also received sodium bicarbonate. C, cocaine bolus; D, 5% dextrose; E, electrocardiographic measurements; H, hemodynamic measurements; NaHCO₃, sodium bicarbonate; PS, programmed ventricular stimulation; VERP, ventricular effective refractory period measurement at all 10 epicardial sites.
TABLE 1. Hemodynamic Effects of Cocaine During Cocaine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Bolus 1</th>
<th>Bolus 2</th>
<th>Bolus 3</th>
<th>NaHCO₃</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>After</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>103±23</td>
<td>88±30</td>
<td>87±24†</td>
<td>69±21†</td>
<td>65±26†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>97±16</td>
<td>90±13†</td>
<td>57±22†</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>8.2±3.7</td>
<td>10.0±5.0</td>
<td>10.2±7.0</td>
<td>10.4±4.2</td>
<td>10.3±6.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.6±6.8</td>
<td>9.6±6.8</td>
<td>5.2±4.8</td>
<td></td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.24±1.29</td>
<td>3.06±1.07*</td>
<td>3.03±0.89†</td>
<td>1.98±0.59†</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.08±0.73†</td>
</tr>
<tr>
<td>SVR (dynes · sec/cm²)</td>
<td>2,065±610</td>
<td>2,480±1,025</td>
<td>2,427±854</td>
<td>2,937±1,146</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>2,290±1,718</td>
<td></td>
</tr>
<tr>
<td>PVR (dynes · sec/cm²)</td>
<td>136±64</td>
<td>220±86*</td>
<td>262±100*</td>
<td>344±152*</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>224±184*</td>
<td></td>
</tr>
<tr>
<td>CBF (ml/min)</td>
<td>16.6±14.1</td>
<td>9.4±7.2*</td>
<td>10.2±8.0*</td>
<td>6.7±4.2*</td>
<td>7.8±6.1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4±1.0</td>
<td>3.4±1.0</td>
<td>3.9±5.24</td>
<td></td>
</tr>
<tr>
<td>CVR (mm Hg · min/ml)</td>
<td>8.6±2.9</td>
<td>11.8±6.2</td>
<td>10.9±6.5</td>
<td>17.7±10.5*</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>19.1±16.4*</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD.

MAP, mean arterial pressure; PAP, mean pulmonary artery pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; CBF, coronary blood flow; CVR, coronary vascular resistance; NA, not available.

*p<0.0001 vs. baseline; †p<0.0001 vs. baseline and after bolus 1; §p<0.0001 vs. baseline and after bolus 2 or 3.

intervals; and QRS duration compared with baseline (p<0.0001) (Table 2). Sinus cycle length and PR, QT, QTc, JT, and JTc intervals continued to lengthen during the cocaine infusion. The effects of cocaine on QRS duration were more transient, with each bolus of cocaine producing an increase in the QRS duration followed by a return to baseline (Table 2). The mean monophasic action potential duration increased from 233±35 at baseline to 291±30 msec after the third cocaine bolus (p<0.05). No afterdepolarizations were observed; however, only a single epicardial site was monitored.

The ventricular effective refractory periods increased significantly from 159±15 at baseline to 177±20 msec after the first cocaine bolus (p<0.05) (Table 3). The dispersion of refractory periods among the 10 electrode sites increased significantly after cocaine administration when measured by either the F ratio (p<0.05) or percent dispersion (p<0.05). An example of refractory period dispersion after cocaine administration is shown in Figure 2. There was no difference between mean cocaine serum concentration measured 5 minutes after the first bolus (4.8±2.2 µg/ml) and that before the second bolus (4.2±1.8 µg/ml) (Table 2), demonstrating that cocaine concentrations were stable during determination of the ventricular effective refractory periods.

Non-sustained monomorphic ventricular tachycardia occurred spontaneously in two dogs. One dog had

TABLE 2. Electrocardiographic Effects of Cocaine During Cocaine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Bolus 1</th>
<th>Bolus 2</th>
<th>Bolus 3</th>
<th>NaHCO₃</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>After</td>
</tr>
<tr>
<td>SCL (msec)</td>
<td>486±82</td>
<td>578±80*</td>
<td>639±80†</td>
<td>650±84*</td>
<td>678±104*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>698±173*</td>
<td>660±130*</td>
<td></td>
</tr>
<tr>
<td>PR (msec)</td>
<td>115±25</td>
<td>139±27*</td>
<td>136±30*</td>
<td>141±18*</td>
<td>148±21*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150±19*</td>
<td>135±22</td>
<td>156±28*</td>
</tr>
<tr>
<td>QT (msec)</td>
<td>256±22</td>
<td>317±41*</td>
<td>324±47*</td>
<td>341±42*</td>
<td>346±48*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>358±48*</td>
<td>350±10</td>
<td>373±52*</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>369±25</td>
<td>426±37*</td>
<td>404±41*</td>
<td>435±41*</td>
<td>421±39*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>433±48*</td>
<td>424±12</td>
<td>454±31*</td>
</tr>
<tr>
<td>JT (msec)</td>
<td>199±22</td>
<td>235±41*</td>
<td>255±43*</td>
<td>250±42*</td>
<td>260±38*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>260±45*</td>
<td>261±11</td>
<td>307±55§</td>
</tr>
<tr>
<td>JTc (msec)</td>
<td>286±23</td>
<td>315±36*</td>
<td>318±38*</td>
<td>317±33*</td>
<td>316±34*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>313±37*</td>
<td>306±9</td>
<td>366±28§</td>
</tr>
<tr>
<td>QRS (msec)</td>
<td>57±4</td>
<td>82±11*</td>
<td>69±8†</td>
<td>92±18‡</td>
<td>87±19*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98±14</td>
<td>89±14</td>
<td>70+9‡</td>
</tr>
<tr>
<td>MAPD (msec)</td>
<td>233±35</td>
<td>252±33</td>
<td>264±30</td>
<td>269±30</td>
<td>281±38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>291±30</td>
<td>291±30‡</td>
<td>299±42</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.35±0.02</td>
<td>7.33±0.03</td>
<td>7.31±0.05</td>
<td>7.32±0.05</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>7.51±0.13*</td>
<td></td>
</tr>
<tr>
<td>Cocaine conc. (µg/ml)</td>
<td>0</td>
<td>4.8±2.2</td>
<td>4.2±1.8</td>
<td>8.8±3.2</td>
<td>9.8±2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>12.2±5.6</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD.

# Top number under NaHCO₃/D₅W refers to the 11 dogs that received sodium bicarbonate; bottom number refers to the four dogs that received dextrose.

SCL, sinus cycle length; MAPD, monophasic action potential duration; NA, not available.

*p<0.0001 vs. baseline; †p<0.0001 vs. baseline and after bolus 1; §p<0.0001 vs. baseline and after bolus 2 or 3; ¶p<0.0001 vs. baseline and after bolus 2; ||p<0.0001 vs. baseline and after bolus 3; *p<0.05 vs. baseline.
six beats of nonsustained ventricular tachycardia at a cycle length of 280 msec that occurred after the first bolus of cocaine and did not recur with subsequent boluses of cocaine. In the other dog, nonsustained ventricular tachycardia occurred after a third cocaine bolus and lasted 11 beats at a cycle length of 220 msec. Sustained ventricular arrhythmias did not occur spontaneously in any dog. Programmed stimulation induced sustained ventricular tachycardia in five dogs and nonsustained ventricular tachycardia in two dogs. The ventricular tachycardia was monomorphic in six dogs and was polymorphic in one. The cycle lengths of the inducible ventricular tachycardia ranged from 230 to 390 msec (mean, 290±68 msec). The induced ventricular tachycardia quickly degenerated to ventricular fibrillation in two dogs. Four dogs had neither spontaneous nor inducible ventricular tachycardia. None of the four control dogs had spontaneous ventricular tachycardia during cocaine infusion. The presence or absence of ventricular arrhythmias (either spontaneous or induced) did not correlate with any hemodynamic, electrocardiographic, or electrophysiological parameter (Table 4).

**TABLE 3. Effects of Cocaine on Ventricular Refractoriness**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Cocaine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERP (msec)</td>
<td>159±15</td>
<td>177±20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% dispersion</td>
<td>11.1±5.7</td>
<td>19.5±4.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>F ratio</td>
<td>3.4</td>
<td>3.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are mean±SD.

VERP, ventricular effective refractory period.

**TABLE 4. Comparison of Electrocardiographic, Electrophysiological, and Hemodynamic Variables in Dogs With and Without Arrhythmias After Cocaine Administration**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arrhythmias</th>
<th>No arrhythmias</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS (msec)</td>
<td>98±19</td>
<td>77±15</td>
<td>NS</td>
</tr>
<tr>
<td>QT (msec)</td>
<td>344±26</td>
<td>343±71</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>68±18</td>
<td>73±29</td>
<td>NS</td>
</tr>
<tr>
<td>CVR (mm Hg⋅min/ml)</td>
<td>7.32±0.05</td>
<td>8.3±8.1</td>
<td>NS</td>
</tr>
<tr>
<td>MAPD (msec)</td>
<td>283±38</td>
<td>267±38</td>
<td>NS</td>
</tr>
<tr>
<td>VERP (msec)</td>
<td>179±11</td>
<td>177±31</td>
<td>NS</td>
</tr>
<tr>
<td>Δ% dispersion</td>
<td>16.6±4.4</td>
<td>21.0±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>F ratio</td>
<td>1.99</td>
<td>0.982</td>
<td>NS</td>
</tr>
<tr>
<td>Cocaine concentration (µg/ml)</td>
<td>9.4±3.3</td>
<td>11.1±3.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean±SD.

MAP, mean arterial pressure; CVR, coronary vascular resistance; MAPD, monophasic action potential duration; VERP, ventricular effective refractory period; Δ% dispersion = % dispersion cocaine minus % dispersion baseline.

**Effects of Sodium Bicarbonate**

Compared with baseline, cocaine did not produce a significant change in arterial pH; however, sodium bicarbonate significantly increased arterial pH from 7.32±0.05 after the second cocaine bolus to 7.51±0.13 after sodium bicarbonate administration (p<0.0001 versus baseline) (Table 2). Sodium bicarbonate did not reverse any of the hemodynamic effects of cocaine (Table 1). Similarly, sodium bicarbonate had no significant effect on reversing cocaine-induced prolongation of sinus cycle length, PR, QT, QTc, and JTc intervals or monophasic action potential duration (Table 2).

In contrast, sodium bicarbonate significantly shortened cocaine-induced QRS prolongation to near that measured at baseline. Mean QRS duration decreased significantly from 98±14 after the third cocaine bolus to 70±9 msec after sodium bicarbonate administration (p<0.0001). This decrease was dramatic and immediate. An example is given in Figure 3. The QRS duration in control dogs given dextrose did not change and was significantly different (p<0.05) from that observed after sodium bicarbonate administration (Figure 4). The mean serum cocaine concentration was 9.8±2.9 before and 12.2±5.6 µg/ml after sodium bicarbonate administration; therefore, the abrupt shortening of QRS duration cannot be explained by a decrease in cocaine serum concentration. Of note, one dog with inducible sustained ventricular tachycardia converted to sinus rhythm immediately after the administration of sodium bicarbonate. Further attempts to induce ventricular tachycardia in this dog after sodium bicarbonate administration were not successful. The effects of cocaine and sodium bicarbonate on the surface electrocardiogram of this dog are shown in Figure 5. When all ventricular arrhythmias, spontaneous and induced, sustained and nonsustained were analyzed, seven of 15 dogs had ventricular tachycardia after cocaine administration alone, whereas only
Effects of sodium bicarbonate on the cocaine action.

Panel C: Reversal of prolonged QRS duration after sodium bicarbonate administration.

three of 10 dogs had ventricular tachycardia after cocaine and sodium bicarbonate (p<0.05).

Discussion

Widespread use of cocaine in the United States has led to an increased awareness of the cardiovascular morbidity and mortality associated with its use,3–9 but the pathophysiological mechanisms of these events are unclear. Previous investigations into the effects of cocaine have produced conflicting data that reflect both the complex pharmacological actions of cocaine and differences in experimental design. Cocaine has direct effects stemming from its local anesthetic properties and indirect effects mediated through the central and autonomic nervous systems.11 Differences in experimental design, that is, the animal model used, whether the experiment was in vitro or in vivo, whether the animal was awake or unconscious, the type of anesthetic used, the dose of cocaine administered, or the rate of cocaine administration, may emphasize different aspects of cocaine’s properties resulting in diverse responses. The experimental model used in this study was designed to examine the effects of repeated high doses of cocaine in an anesthetized canine model.

Effects of Cocaine on Hemodynamics

High-dose intravenous cocaine produced dose-dependent decreases in arterial blood pressure and cardiac output. Previous studies reported that low-dose cocaine increased cardiac output and blood pressure in conscious experimental animals18,19 and humans20; however, a recent study using an isolated dog heart preparation found that cocaine produced a dose-dependent decrease in contractility.21 High doses of intravenous cocaine administered rapidly also decreased indexes of left ventricular function in intact dogs.22 At high doses, then, the cardiodepressant effect of cocaine may override its sympathomimetic effects.23

The decrease in coronary blood flow that was observed after cocaine administration is also consistent with that seen by other investigators. Cocaine has been noted to cause vasoconstriction of vascular smooth muscle in vitro,23 to decrease coronary artery cross-sectional area and coronary blood flow, and to increase coronary vascular resistance in dogs22,24,25 and humans.26 Despite the significant decreases in coronary blood flow and increases in coronary artery resistance produced by cocaine in the present study, electrocardiographic evidence of ischemia or infarction was not observed.

Effects of Cocaine on Electrophysiology

In this study, cocaine caused dose-dependent increases in sinus cycle length. Recent intracellular work demonstrated that cocaine causes concentration-dependent depression in sinus node automaticity.10 In humans, although low doses of cocaine may cause catecholamine-related sinus tachycardia,27,28 higher doses as used here and by others22 cause sinus node depression.

The other electrophysiological effects of cocaine appear to be similar to those produced by type I antiarrhythmic agents.10 Cocaine significantly slowed cardiac conduction as measured by its effects on prolonging the PR interval and QRS duration. Because these electrocardiographic changes occurred in the setting of decreasing heart rate, they were unlikely to be due to rate-dependent effects of cocaine. In addition, the effects of cocaine on the QT interval, action potential duration, and ventricular effective refractory period indicate that repolarization was also prolonged. In animal models, cocaine has significantly prolonged the PR, QT, AH, and HV intervals and increases the QRS duration.29–32

In contrast to the dose-dependent effects of cocaine on sinus cycle length and on PR and QT intervals, the ability of cocaine to prolong the QRS duration was more transient. This may indicate either a brief duration of sodium channel blockade by cocaine or rapid distribution of cocaine out of the conduction tissue compartment. Similar results were obtained by Kabas et al,29 who found that the HV interval returned to baseline within 15 minutes of cocaine bolus administration.

Although cocaine is widely perceived as being arrhythmogenic, there are only scattered reports of cocaine-related arrhythmias occurring in the absence of ischemia.6–9,12,33 Inoue and Zipes12 recently showed in an animal model that cocaine appeared to
be arrhythmogenic only when combined with experimentally induced infarction and norepinephrine infusion. In the present study, spontaneous sustained ventricular arrhythmias did not occur after cocaine intoxication; however, ventricular tachycardia could be induced in a number of animals. A less-aggressive stimulation protocol was used to increase the specificity of ventricular arrhythmias that were induced. Although induction of ventricular tachycardia was not attempted before cocaine administration, normal dogs probably would not have had inducible ventricular tachycardia with the stimulation protocol that was used. Thus, it may be that although cocaine causes profound changes in the electrophysiological milieu, these are only manifested as arrhythmias under the influence of some other factor such as programmed stimulation, ischemia, or high sympathetic tone.

The mechanism of the ventricular arrhythmias that were observed is not known, but the presence of slowed conduction, increased refractoriness, increased dispersion of refractoriness, and inducibility by programmed stimulation is consistent with reentry. Although some of these characteristics are also consistent with triggered activity and although the observed increase in sinus cycle length would be expected to enhance the likelihood of early afterdepolarizations, afterdepolarizations were not observed in the single monophasic action potential monitored. Of course, this finding does not exclude the possibility that they were present at other sites. Interestingly, although cocaine caused quinidine-like delays in repolarization, no episodes of spontaneous torsades de pointes were observed.

**Effects of Sodium Bicarbonate**

Historically, sodium lactate or sodium bicarbonate has been used successfully to reverse the conduction defects and arrhythmias associated with intoxication from type Ia antiarrhythmic drugs and other drugs with sodium channel-blocking properties such as tricyclic antidepressants. Because preliminary evidence from previous studies and the present study suggest that cocaine also has potent type I antiarrhythmic activity, the efficacy of sodium bicarbonate as an antidote to the cardiovascular effects of cocaine was evaluated. In contrast to the ability of sodium bicarbonate to increase blood pressure when used for tricyclic antidepressant overdose, sodium bicarbonate had no significant effect on reversing any of the hemodynamic effects of cocaine. This could be due to either the magnitude of cocaine intoxication or the reported cardiodepressant effects of sodium bicarbonate.

Similar to its effects in both type Ia antiarrhythmic and tricyclic antidepressant overdose, sodium bicarbonate had a dramatic effect on reversing the QRS prolongation produced by cocaine, promptly returning the QRS duration to near baseline value. Sodium bicarbonate had no effect on reversing cocaine-induced prolongation in sinus cycle length, PR, QT, QTc, JT, or JTc intervals. Furthermore, ventricular arrhythmias, both spontaneous and induced, occurred less frequently after sodium bicarbonate administration.

Several mechanisms may be responsible for the ability of sodium bicarbonate to reverse the conduction defects and arrhythmias associated with drugs having type I properties. Increases in serum sodium concentration may increase the gradient for the inward movement of sodium ions across cardiac cell membranes and thus antagonize the tricyclic antidepressant-induced blockade of sodium channels. Second, the pH-dependent actions of drugs with type I antiarrhythmic activity are well known; acidosis
tends to accentuate and alkalosis to attenuate their electrophysiological actions.\textsuperscript{45-48} Third, a decrease in extracellular potassium concentration due to alkalization has been thought to contribute to reversal of tricyclic antidepressant conduction delays, although preliminary data does not seem to support this hypothesis.\textsuperscript{37} Last, the increase in pH produced by sodium bicarbonate may also increase the protein binding of amitriptyline with a subsequent decrease in the free, pharmacologically active form of the drug.\textsuperscript{48} Cocaine has been shown to be approximately 90\% protein bound in human serum.\textsuperscript{49} At this time, it is not known whether sodium bicarbonate reversal of QRS prolongation secondary to cocaine is due to one or a combination of these factors.

Interestingly, the efficacy of sodium bicarbonate therapy in cocaine intoxication has already been noted. Jonsson et al.\textsuperscript{50} reported a patient who had an accelerated idoventricular rhythm and profound acidosis after massive cocaine overdose. The patient’s electrocardiogram normalized after he was given sodium bicarbonate to treat the acidosis. This case report mirrors what was observed in the present study and provides preliminary evidence for the clinical use of sodium bicarbonate to reverse the conduction delays that can be seen with ingestion of large quantities of cocaine.

Conclusion

In conclusion, high doses of intravenous cocaine produce dose-dependent decreases in blood pressure, cardiac output, and coronary blood flow in anesthetized dogs. Cocaine also significantly prolongs sinus cycle length, PR, QT, and QTc intervals and increases the QRS duration. Dispersion of ventricular effective refractory periods is also increased by cocaine. Spontaneous ventricular arrhythmias were uncommon, suggesting that cocaine-related arrhythmias may be more likely to occur in the setting of some other cocaine-induced condition, such as ischemia. Sodium bicarbonate selectively reverses cocaine-induced QRS prolongation and may be a useful antidote in the setting of cocaine overdose complicated by slowed ventricular conduction. Further investigation (particularly at the cellular level) is required to elucidate the mechanism(s) of sodium bicarbonate’s ability to reverse cocaine-induced conduction defects.

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References


**KEY WORDS** • arrhythmia • conduction • sudden cardiac arrest • cocaine • sodium bicarbonate
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