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Acute Cocaine Intoxication in the Conscious Dog: Studies on the Mechanism of Lethality[1]

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ABSTRACT

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Cocaine HCl was administered (0.5 mg/kg/min i.v.) to conscious mongrel dogs until death (N = 17; mean lethal dose, MLD: 22 ± 2 mg/kg). All animals exhibited significant increases in mean arterial pressure, heart rate, cardiac output and rectal temperature, while arterial pH decrease significantly from predrug control levels. Chlorpromazine pretreatment (12 mg/kg i.v.; N = 6) antagonized all responses induced by a potentially lethal cocaine challenge of 39.5 mg/kg (MLD + 3 S.D.) and all animals survived a 48-hr observation period. Animals pretreated with propranolol (6 or 10 mg/kg i.v.; N = 5) prior to a similar cocaine challenge exhibited partial reduction of the cocaine-induced cardiovascular changes; however, all animals convulsed and died (MLD: 20 ± 1 mg/kg). Pretreatment with pancuronium before the cocaine challenge prevented both acidemia and hyperthermia but had no effect on the cocaine-induced changes In cardiovascular parameters; all animals (N = 6) survived. Diazepam pretreatment (3–5 mg/kg i.v.; N = 6) prevented the increase in rectal temperature, the decrease in arterial pH and moderated the cocaine-induced changes in the cardiovascular parameters measured; all animals survived the cocaine challenge. Animals pretreated with pimozide (6 mg/kg i.v.; N = 4) convulsed and died similarly to untreated controls (MLD: 23 ± 2 mg/kg). The relative importance of arterial acidemia in cocaine death was determined in another group of dogs (N = 3) in which arterial pH was maintained within the physiologically normal range throughout the cocaine infusion. All animals convulsed and died with significantly elevated rectal temperature levels (MLD = 18 ± 2 mg/kg). The contribution of hyperthermia to the lethal process was studied in two groups of animals that received the potentially lethal cocaine challenge at either 5°C or −5°C ambient temperature. Eight of 14 animals tested at 5°C survived with significantly reduced rectal temperature levels; all animals tested at −5°C (N = 5) survived and mean rectal temperature in this group declined an average of 6.6 ± 1.1°C from predrug control levels. These data indicate that hyperthermia is the most important contributor to cocaine death in this species.

Recently, we reported on the pathophysiologic changes resulting from a lethal infusion of cocaine administered acutely to conscious dogs (Catravas *et al.*, 1978). In these experiments, conscious dogs received cocaine HCl i.v. until death (0.5 mg/kg/min; 0.82 ml/min). All animals convulsed and died approximately 42 min after the beginning of the cocaine infusion. At the time of death, all animals exhibited significant increases in mean arterial pressure, cardiac output, heart rate and rectal temperature, while arterial pH levels were significantly reduced from predrug control levels. We concluded that death could have resulted from a single effect or a combination of the cardiotoxic, acidemic or hyperthermic effects of cocaine, but we were unable to distinguish the exact cause of death in those experiments.

The studies reported here were undertaken to clarify the contribution to the lethal process of the aforementioned cocaine-induced physiologic changes. In addition, since illicit cocaine use appears to increase continuously, these experiments were also aimed at describing pharmacologic agents with potential usefulness as clinical antidotes of cocaine poisoning. To evaluate the cardiotoxic actions of cocaine, animals were pretreated with propranolol, a *beta* adrenergic receptor antagonist (Adam *et al.*, 1973; Andres *et al.*, 1974); the contribution of acidemia to cocaine death was examined by infusing animals with dilute NaOH at doses that maintained physiologically normal arterial pH values. Since convulsive exertions are known to induce hyperthermia, another group of animals received pancuronium at doses that produced complete neuromuscular block (Buckett *et al.*, 1968); other animals were exposed to a cold environment during cocaine infusion. Two additional groups of animals were used to test the antidotal properties of chlorpromazine and diazepam; chlorpromazine has been shown to antagonize amphetamine poisoning in the dog (Catravas *et al.*, 1977) and both drugs possess powerful tranquilizing actions (Janssen *et al.*, 1968; Stripling and Ellinwood, 1976). Further-

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more, to distinguish between the sedative and anticatecholaminergic properties of chlorpromazine, animals were pretreated with pimozide at doses that produce dopamine receptor blockade without sedation (Janssen *et al.*, 1968).

Methods

The procedures employed in these studies have been described earlier by Catravas *et al.* (1978).[3] In brief, the animals used were adult mongrel dogs of either sex weighing an average of 11 ± 2 kg (range: 7.2–15.1 kg). They were housed in indoor heated kennels with exercise runs which were illuminated on a 12/12 hr light-dark cycle. Food (Purina Dog Chow) was supplied daily in proportion to the weight of the animals. Each animal was placed in the supine position on a specially constructed operating table and restrained gently with soft leather binders around the legs; care was taken at all times to assure that the animals experienced only minimal discomfort. Under local anesthesia (1.5% procaine), the femoral vessels were exposed; cannulas were introduced to the right atrium and the thoracic aorta *via* these vessels. Control measurements of arterial systolic and diastolic blood pressures, cardiac output and heart rate were then obtained; arterial blood was withdrawn for the measurement of pH, pCO_2 and pO_2; rectal temperature was recorded by means of a thermistor. When appropriate (see protocol below), animals were tracheostomized under local infiltration with 1.5% procaine. All studies were carried out at room temperature, unless otherwise indicated. The following protocol was employed:

Group 1: received cocaine HCl (0.5 mg/kg/min i.v.; 0.82 ml/min) until death ($N = 17$). In all subsequent groups, cocaine was similarly infused until death or until a total dose of 39.5 mg/kg (79 min of infusion; LD_{100}) was achieved. This dose is three standard deviations greater than the average lethal dose of cocaine as determined in Group 1.

Group 2: received propranolol (6 or 10 mg/kg i.v.) 2 hr before cocaine infusion. Two dogs received 6 mg/kg and three received 10 mg/kg of propranolol; since all animals responded similarly to cocaine regardless of the dose of propranolol, results from all dogs were treated collectively to facilitate interpretation of the data ($N = 5$).

Group 3: received chlorpromazine (12 mg/kg i.v.) 1 hr before cocaine ($N = 6$).

Group 4: received pancuronium at individually adjusted doses that produced respiratory paralysis (approximate dose: 0.5 mg/kg i.v.). All animals were respired artificially *via* a tracheal cannula implanted under local anesthesia (respiratory frequency, 18/min; tidal volume, 150 ml) by means of a Harvard Ventilator (Harvard Apparatus, Millis, MA). Cocaine infusion began immediately after respiratory paralysis was achieved ($N = 6$).

Group 5: received cocaine as did animals in Group 1; however, during the cocaine infusion, NaOH (0.05–0.5 N in saline) was administered i.v. at doses sufficient to maintain physiologically normal arterial pH levels throughout the experiment ($N = 3$).

Group 6: these animals received cocaine in a variable temperature chamber (Hotpack Corp., Philadelphia, PA) adjusted to 5°C ($N = 14$).

Group 7: received cocaine in an ambient temperature of −5°C ($N = 5$).

Group 8: received pimozide (6 mg/kg i.v.) 2 hr before cocaine ($N = 4$).

Group 9: received diazepam (3–5 mg/kg i.v.) approximately 1 hr before cocaine administration. Each animal was individually titrated with diazepam until sedation was achieved ($N = 6$).

[3] The procedures employed in the surgical preparation of the animals used in these experiments conformed to the standards for animal care endorsed by the American Physiological Society and were approved by the Animal Welfare Committees of both the School of Pharmacy and the University of Mississippi.

In each treatment group, all parameters were measured before any drug administration (cocaine or pretreatment) and at 10-min intervals after the beginning of cocaine infusion.

All surviving animals were kept on the operating table for at least 3 hr after the termination of the cocaine infusion. Surgical wounds were then sutured, ampicillin was administered i.m. and the animals were returned to their cages where they were observed for an additional 24 hr. At the end of this period, they were sacrificed and autopsied.

Statistical evaluations were carried out between the control group (cocaine alone, Group 1) and the treatment groups (Groups 2–9). Measurements in the treatment groups were compared to the corresponding measurements of Group 1 (*i.e.*, at 0-, 10-, 20-, 30- and 40-min measurements) by means of Student's t test for independent samples (Senter, 1969). Means were considered significantly different when $P < .01$. All computations were performed with the aid of a Decksystem-10 computer.

Results

A detailed analysis of the effects of a lethal infusion of cocaine acutely administered to a conscious dog (Group 1) has appeared earlier (Catravas *et al.*, 1978).

Effects of Pretreatment with Propranolol, Chlorpromazine or Pancuronium on Cocaine-Induced Lethality and Changes in Physiologic Parameters.

Lethality. Propranolol-pretreated dogs (Group 2) evidenced behavioral stimulation and convulsions similar to the cocaine controls (Group 1). The mean convulsive threshold dose (*i.e.*, the dose of cocaine at the time convulsions began) was 8.5 ± 2 mg/kg (11.8 ± 1.4 mg/kg for Group 1). The animals died at a mean lethal dose (MLD) of 19.5 ± 1 mg/kg (MLD for Group 1: 21 ± 2 mg/kg). Chlorpromazine-pretreated animals convulsed mildly at a significantly higher dose of cocaine (21.6 ± 3 mg/kg; $P < .01$) when compared to Group 1. All chlorpromazine- and pancuronium-treated dogs survived the LD_{100} of cocaine (39.5 mg/kg).

Cardiovascular parameters. Propranolol pretreatment prevented the cocaine-induced increases in mean arterial pressure, heart rate and cardiac output (fig. 1). Mean arterial pressure and heart rate were significantly lower than the corresponding values in Group 1 ($P < .01$) at the 30- and 40-min measurements, while cardiac output values were significantly reduced at the 20-, 30- and 40-min measurements. Chlorpromazine-pretreated animals exhibited mean arterial pressure, heart rate and cardiac output values that were significantly lower than those in the cocaine controls at the 10-, 20-, 30- and 40-min determinations ($P < .01$). These parameters remained at approximately the same levels for the subsequent 50 min of observations (fig. 1). No significant differences from the mean arterial pressure, heart rate and cardiac output values in Group 1 were observed in the pancuronium-pretreated dogs at any time (fig. 1).

Arterial pH and rectal temperature. Propranolol pretreatment failed to prevent the pronounced cocaine-induced arterial acidemia and hyperthermia. Indeed, arterial pH and rectal temperature responses to cocaine were identical between the control (Group 1) and the propranolol-treated animals (Group 2) at all measurement times (fig. 1). However, all chlorpromazine- and pancuronium-treated animals exhibited arterial pH and rectal temperature levels that were significantly lower than those in the cocaine controls ($P < .01$; fig. 1). Consequently, arterial pH in Groups 3 and 4 remained at physiologically normal levels throughout the experiment,

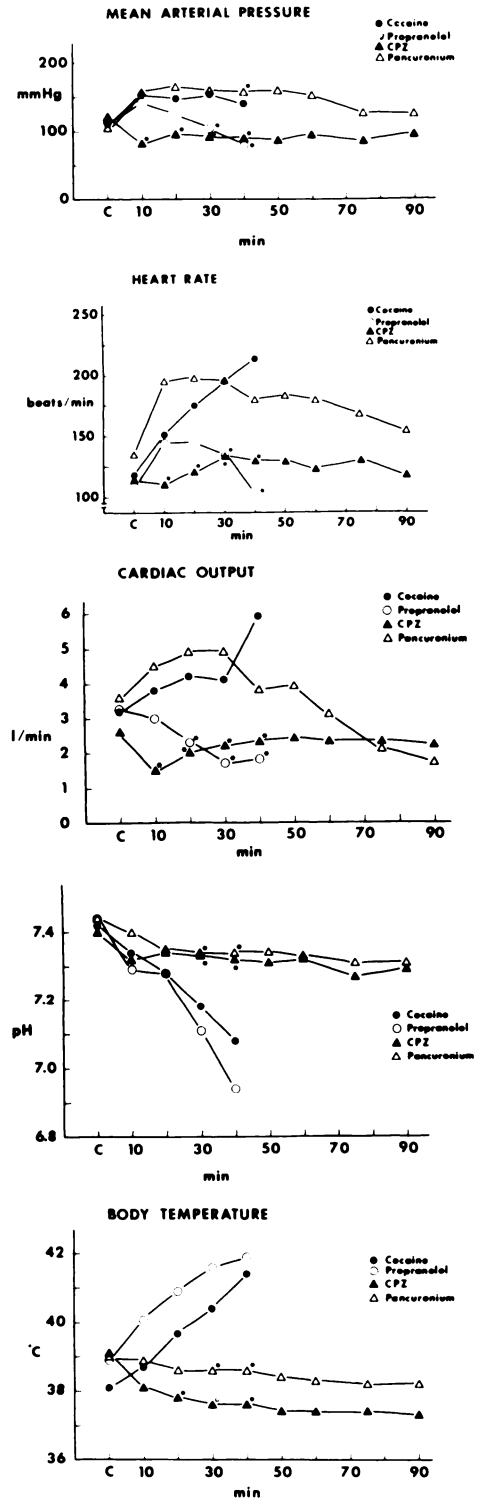

Fig. 1. Average changes in mean arterial pressure, heart rate, cardiac output, arterial pH and body (rectal) temperature induced by a lethal infusion of cocaine to untreated (●, N = 17), propranolol (○, N = 5)-, chlorpromazine (▲, N = 6)- and pancuronium (△, N = 6)-pretreated conscious dogs. The abscissa shows the predrug control determination (C) and the time (min) after the beginning of cocaine infusion. Cocaine administration (0.5 mg/kg/min; 0.82 ml/min i.v.) lasted until either the animal died or had received 39.5 mg/kg. Asterisks (*) represent significant difference ($P < .01$) from the corresponding averages of the untreated group. CPZ, chlorpromazine.

whereas rectal temperature decreased below predrug control values.

Effects of Arterial pH Stabilization on the Cocaine-Induced Lethality and Changes in Rectal Temperature

Lethality. All animals which received NaOH during the cocaine infusion (Group 5) convulsed violently (mean convulsive threshold dose: 10 ± 1 mg/kg) and died (MLD: 18 ± 2 mg/kg). These values were statistically identical to those in Group 1. However, arterial pH values in this group remained within the physiologically normal range and were significantly higher than the corresponding values in the cocaine control group at all times ($P < .01$; fig. 2).

Rectal temperature. Despite the NaOH, cocaine administration to the dogs in Group 5 produced a severe hyperthermic response which was statistically identical to the response seen in Group 1 (fig. 2). Cardiovascular parameters were not measured in this group or in Groups 6 and 7.

Effects of Low Ambient Temperature on the Cocaine-Induced Lethality and Changes in Rectal Temperature

Fourteen animals (Group 6) were administered cocaine in an ambient temperature of 5°C. Six dogs in this group died at a MLD of 32 ± 3 mg/kg of cocaine ($P < .01$ compared to Group 1), while eight animals survived the LD_{100} of cocaine (39.5 mg/kg). Arterial pH values in both groups of animals were significantly higher than those in the cocaine control group at the 40-min measurement (table 1). Similarly, mean rectal temperature in all dogs of Group 6 was significantly reduced at both the 30- and 40-min measurements (table 1); however, rectal temperature in the six animals that died remained at or slightly above predrug control levels, whereas in the eight survivors mean values for this parameter reached significantly hypothermic levels (34.2°C at the 170-min measurement; table 1).

Animals in Group 7 were administered cocaine at an ambient temperature of −5°C; all animals in this group survived the LD_{100} of cocaine. Rectal temperature values were significantly lower when compared to Group 1 at the 30- and 40-min measurements and continued to decline until a mean minimum value of 32.7 ± 1.2°C was recorded at the 140-min measurement (fig. 2). To assure that the pronounced hypothermia observed in this group was a cocaine-induced effect, untreated conscious dogs (N = 3) were placed in −5°C ambient temperature and their rectal temperatures were monitored; the mean maximal decline recorded after 140 min was 0.4°C.

Lethality. An alternate expression of the lethality data collected from Groups 1, 6 and 7 is presented in figure 2 which describes the relationship between percentage of lethality and the ambient temperature at which cocaine is administered. Thus, the dose of cocaine which is lethal to all animals tested at 22°C would kill only 50% of the animals if administered at an ambient temperature of 8°C. In addition, the correlation between ambient temperature and cocaine-induced changes in rectal temperature is presented in the lower panel of figure 2. Accordingly, if a group of dogs received a lethal dose of cocaine at an ambient temperature of 11.5°C, certain animals would exhibit hyperthermia and die, while others would become hypothermic and live, but the expected *average* change in rectal temperature from predrug control levels would be zero.

Effects of Pretreatment with Pimozide or Diazepam on Cocaine-Induced Lethality and Changes in Physiologic Parameters

Experiments in Group 3 demonstrated that chlorpromazine is an effective antagonist of cocaine-induced death, with poten-

tial clinical antidotal use. At the dose employed in this study (12 mg/kg i.v.), chlorpromazine posesses a variety of actions: in the periphery, it is an effective antagonist of vascular *alpha* adrenergic and dopaminergic receptors; these blocking properties are also present in the central nervous system where, additionally, chlorpromazine exerts significant sedative effects (Janssen *et al.*, 1968). To further investigate the possibilities of alternate potential antidotes, the experiments in Groups 8 and 9 were carried out utilizing pimozide, a central antidopaminergic agent with no appreciable sedative actions (Janssen *et al.*, 1968) and diazepam for its pronounced sedative and anticonvulsive effects.

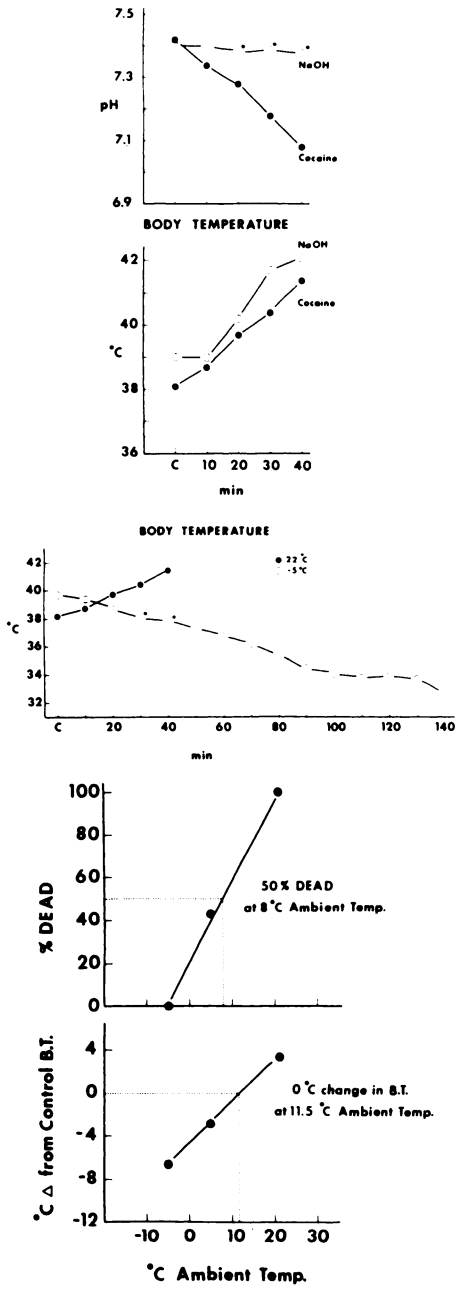

Fig. 2. Upper two panels: average changes in arterial pH or body temperature induced by a lethal infusion of cocaine to untreated (●, N = 17) or NaOH-treated (○, N = 3) conscious dogs. See legend of figure 1 for additional explanations. Middle panel: average changes in body (rectal) temperature induced by a lethal infusion of cocaine to untreated conscious dogs at 22°C (●, N = 17) or −5°C (○, N = 5) ambient temperature. See legend of figure 1 for additional explanations. Lower two panels: average percentage of lethality or averages of maximal changes from predrug control body (rectal) temperature (B.T.) values induced by a lethal infusion of cocaine administered at −5°C (N = 5), 5°C (N = 14) or 22°C (N = 17). Cocaine administration (0.5 mg/kg/min; 0.82 ml/min i.v.) lasted until either the animal died or had received 39.5 mg/kg.

TABLE 1

The effects of cocaine (0.5 mg/kg/min i.v.) administered at 5°C ambient temperature (T) on arterial pH or rectal temperature in the conscious dog[a]

	Died (N = 5)[b]		Lived (N = 6)[c]	
	pH	Rectal T	pH	Rectal T
min		°C		°C
C[d]	7.358 ± 0.008	39.6 ± 0.2	7.400 ± 0.016	39.5 ± 0.1
10	7.328 ± 0.035	38.9 ± 0.2	7.350 ± 0.026	38.5 ± 0.2
20	7.312 ± 0.033	38.6 ± 0.3	7.334 ± 0.031	38.6 ± 0.3
30	7.304 ± 0.027	38.6 ± 0.3*	7.319 ± 0.031*	38.6 ± 0.4*
40	7.285 ± 0.032*	38.9 ± 0.5*	7.307 ± 0.028*	38.7 ± 0.5*
50	7.213 ± 0.041	39.1 ± 0.8	7.280 ± 0.031	38.5 ± 0.6
60	7.235 ± 0.012	38.5 ± 1.3	7.176 ± 0.038	38.2 ± 0.7
70			7.308 ± 0.018	37.8 ± 0.8
90			7.280 ± 0.019	37.3 ± 0.7
100				36.6 ± 0.8
110				35.0 ± 1.0
120				35.8 ± 1.1
130				35.2 ± 1.1
140				34.8 ± 0.8
160				34.6 ± 1.0
170				34.2 ± 0.8
180				35.6 ± 1.0
190				34.8 ± 1.1
200				36.1 ± 2.0

[a] Values represent the mean ± S.E. (Group 6); asterisks (*) represent significant difference ($P < .01$) from the corresponding means of Group 1.

[b] These animals died after receiving an average dose of 32 ± 3 mg/kg of cocaine.

[c] These animals survived 39.5 mg/kg (LD_{100}) of cocaine; cocaine infusion was terminated at 79 min.

[d] C, control determination; time represents minutes after the beginning of cocaine infusion.

Lethality. Pimozide-pretreated animals (Group 8) convulsed and died at cocaine dose levels that were statistically similar to those in Group 1 (mean convulsive dose: 16 ± 3 mg/kg; MLD: 23 ± 3 mg/kg). Dogs that received diazepam (Group 9) did not convulse and survived the infusion of a LD_{100} of cocaine. However, two of the six animals tested died between 48 and 72 hr after their return to their cages. Postmortem examination of these two animals did not aid in determining the cause of death.

Physiologic parameters. Pimozide pretreatment had no influence on the cocaine-induced responses in most of the parameters measured. Indeed, the only difference observed between Group 8 and Group 1 was a potentiation of the response of the pimozide-treated dogs to the effects of cocaine on mean arterial pressure. These values were significantly elevated at the 10- and 20-min measurements; however, the predrug control values in this group were significantly higher than those in Group 1 ($P < .01$; table 2). Diazepam pretreatment prevented the cocaine-induced changes in mean arterial pressure and heart rate. Mean arterial pressure was signifiantly decreased from the corresponding values in Group 1 at the 10-min measurement; heart rate remained close to predrug control levels throughout the experiment and was significantly different from Group 1 at all measurements (table 2). No significant changes from Group 1 were observed in the cardiac output values. Animals receiving diazepam were also protected against the

TABLE 2

The effects of pimozide (6 mg/kg i.v.; N = 4) or diazepam (3–5 mg/kg i.v.; N = 6) pretreatment on several physiologic parameters in the conscious dog during a lethal infusion of cocaine (0.5 mg/kg/min i.v.)[a]

	MAP[b]	HR	CO	pH	RT
min	*mm Hg*	*bpm*	*l/min*		*°C*
Pimozide					
C[c]	131 ± 5*	114 ± 10	4.31 ± 0.67	7.44 ± 0.01	39.2 ± 0.3
10	175 ± 4*	128 ± 6	3.59 ± 0.37	7.39 ± 0.01	39.7 ± 0.6
20	180 ± 4*	151 ± 8	4.31 ± 0.41	7.41 ± 0.01*	40.1 ± 0.6
30	178 ± 17	205 ± 22	5.31 ± 0.82	7.30 ± 0.05	41.0 ± 0.7
40	168 ± 63	155 ± 35	3.16 ± 1.76	7.29 ± 0.19	41.8 ± 1.3
Diazepam					
C	109 ± 6	111 ± 10	3.27 ± 0.52	7.40 ± 0.02	39.1 ± 0.3
10	121 ± 7*	115 ± 10*	2.64 ± 0.66	7.34 ± 0.02	38.6 ± 0.5
20	134 ± 13	119 ± 8*	3.08 ± 0.66	7.31 ± 0.02	38.6 ± 0.5
30	122 ± 7	122 ± 7*	3.06 ± 0.75	7.32 ± 0.02*	38.5 ± 0.6
40	132 ± 10	139 ± 15*	3.50 ± 1.02	7.30 ± 0.03*	38.6 ± 0.6*
50	138 ± 12	143 ± 12	2.55 ± 0.45	7.31 ± 0.02	38.9 ± 0.6
60	146 ± 9	155 ± 24	2.59 ± 0.77	7.29 ± 0.02	39.0 ± 0.8
70	146 ± 8	147 ± 11	2.63 ± 0.62	7.28 ± 0.01	39.4 ± 1.0
90	139 ± 11	155 ± 16	2.40 ± 0.69	7.32 ± 0.01	39.8 ± 1.0

[a] Values represent the mean ± S.E.; asterisks (*) represent significant difference ($P < .01$) from the corresponding means in group 1.
[b] MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; CO, cardiac output; RT, rectal temperature.
[c] C, control determinations; numbers represent time (minutes) after the beginning of cocaine infusion.

cocaine-induced acidemia and hyperthermia. Arterial pH was significantly higher than Group 1 at the 30- and 40-min measurements, while rectal temperature was significantly lower than in the cocaine controls at the 40-min measurement ($P < .01$; table 2).

Discussion

This study has attempted to examine the means by which alterations in the function of different organ systems may contribute to cocaine-induced lethality. The data represent changes occurring during a lethal infusion of cocaine and should not be confused with changes observed after a bolus injection of the drug. Animals receiving a bolus lethal dose of cocaine die within 10 min (Catravas *et al.*, 1978). It is unlikely that either acidemia or hyperthermia could have developed in such a short time interval; instead, death may be hypothesized to ensue from a direct action of cocaine on the heart.

Propranolol. Propranolol pretreatment failed to alter the cocaine-induced excitation, arterial acidemia and hyperthermia in all animals tested. However, systemic pressure declined significantly in this group. This could be the result of a centrally hypotensive action of the drug (Lewis and Haeusler, 1975) or due to the *beta* adrenergic blocking activity of propranolol resulting in decreased heart rate (Adam *et al.*, 1973) and lowered cardiac output (Andres *et al.*, 1974). Alternatively, at least part of the antihypertensive action of propranolol could be derived from the ability of the drug to block renin secretion (Richardson *et al.*, 1974).

The fact that propranolol prevented the cocaine-induced changes in cardiovascular parameters without influencing the changes in arterial pH and rectal temperature may be related to the inability of the drug to prevent cocaine death. Even though Rappolt *et al.* (1976) have claimed propranolol to be a specific antagonist of acute cocaine intoxication in humans, the authors specify that propranolol is recommended in cases of mild cocaine intoxication only (R. I. Rappolt, personal communication).

Chlorpromazine. Cocaine is believed to interact with central dopaminergic neurons (Galambos *et al.*, 1967; Fekete and Borsey, 1971; Wallach and Gershon, 1972; Post, 1975). Chlorpromazine is a known dopamine receptor blocking agent and the antidotal properties exhibited in this study could be related to its antidopaminergic effects. However, at high doses, most neuroleptics posses both antiadrenergic and sedative effects (Janssen *et al.*, 1968). Other data suggest that haloperidol antagonizes cocaine hypermotility and stereotypy only at sedative doses (Simon *et al.*, 1972), whereas lower doses (dopamine blocking) of either haloperidol or α-methyltyrosine which had been proven adequate in antagonizing amphetamine hypermotility and sterotypy appeared to be ineffective in altering similar cocaine-induced responses (Simon *et al.*, 1972; Simon, 1973). The dose of chlorpromazine employed in this study (12 mg/kg i.v.) is large enough to produce pronounced antidopaminergic, antiadrenergic and sedative effects (Janssen *et al.*, 1968); therefore, the antidotal effects of chlorpromazine on cocaine poisoning may depend on more than its antidopaminergic actions.

Although all animals in this group convulsed, the seizures were very mild. As a result, arterial pH remained at predrug control levels and rectal temperature remained at or below predrug control levels throughout the experiment. Other mechanisms responsible for the observed hypothermia could include peripheral vasodilation, slowing of metabolic processes and lowering of blood pressure as well as a central depressant action on the hypothalamus and the reticular formation (Rewerski and Gunulka, 1973). The depressant effects of chlorpromazine on arterial blood pressure and heart rate observed in this study have been reported previously (Angrist *et al.*, 1974).

Pancuronium. Pancuronium is an agent with limited but well defined pharmacological activity. Its only recognized effect is blockade of the neuromuscular junction (Buckett *et al.*, 1968). Because it apparently lacks any other peripheral or central actions, all pancuronium-treated dogs exhibited changes in vascular and cardiac functions comparable to those observed in Group 1. However, effective blockade of the cocaine-induced

changes in arterial pH and rectal temperature were observed, probably due to the absence of muscular activity.

Pimozide. Although the dose of pimozide administered to this group was more than 10 times the antidopaminergic and adrenergic blocking dose of the drug (Janssen *et al.*, 1968), the agent neither prevented lethality nor altered any of the cocaine-induced changes in the parameters monitored. All animals in this group were very excited and convulsed as did animals in Group 1. Since sedation was not observed in pimozide-treated dogs, these data, in agreement with data from Groups 3 and 9, suggest that sedation may be necessary for the prevention of cocaine-induced death.

Diazepam. All animals tested in this group were markedly sedated. Evidence suggests that the sedative actions of the drug are related to its activity on the amygdaloid nucleus or the reticular formation (Wale and Jenkins, 1973; Stripling and Ellinwood, 1976) and this activity of diazepam is believed to be responsible for its anticonvulsive properties (Riblet and Tuttle, 1970; Stripling and Ellinwood, 1976). None of the animals in this group convulsed and thus arterial pH and rectal temperature remained within physiologically normal range.

A puzzling observation in this treatment group is that two of the six animals tested died between 48 and 72 hr after cocaine infusion was terminated. To ensure that the dose of diazepam employed in this study was not toxic, four additional dogs were given the same dose of diazepam and were observed for several days; all animals survived. Postmortem examination of the two animals that died did not reveal any pathologic changes, therefore the reason for these deaths remains unknown.

Mechanisms of lethality. Previous reports on experimental or clinical fatalities due to cocaine intoxication have assumed death to be due to cardiovascular collapse (Young and Glauber, 1947; Thienes and Haley, 1972), ventricular fibrillation (Ruben and Morris, 1952; Jordan *et al.*, 1958) or hyperthermia (Peterson and Hardinge, 1967).

In the present study, we investigated the influence of pharmacologic or physiologic interventions to the cocaine-induced responses in mean arterial pressure, cardiac output, heart rate, arterial pH and rectal temperature. In Groups 1, 2, 5 and 8, all animals died after a lethal infusion of cocaine. The only response common to all animals in these groups was pronounced hyperthermia. Furthermore, all surviving animals in the other treatment groups exhibited rectal temperature values at or below predrug control levels.

Consequently, these experiments demonstrate that hyperthermia apparently is the most important contributor to death after a lethal infusion of cocaine to conscious dogs. Severe hyperthermia has long been recognized as a potential cause of death. Thus, swine die when rectal temperature is increased to 43°C (Marple *et al.*, 1974), rats succumb at core temperatures of 42°C (Hubbard *et al.*, 1977) and mongrel dogs exhibit 100% mortality at rectal temperature of 43°C (Shapiro *et al.*, 1973). All of these values are similar to the core temperatures at the time of death of the animals in Group 1 (42.2 ± 0.2°C).

Hypothermia. Yehuda and Wurtman (1973) reported a hypothermic response to nonlethal doses of amphetamine (15 mg/kg i.p.) when administered to rats at 4–15°C ambient temperature; a central dopaminergic mechanism was postulated for this effect. Additionally, a peripheral mechanism for hypothermia has been proposed, consisting of increased heat loss and slowing of the metabolic activities (Weihe, 1973). Rectal temperature in animals of Group 7 decreased more than 6°C from predrug control values. When untreated control dogs were placed in the same environment, rectal temperature decreased by a maximum of only 0.4°C. In the absence of any pertinent information, one could only speculate that any of the aforementioned central or peripheral mechanisms could participate in bringing about the hypothermic effects observed in this study.

The lack of a uniform hypothermic response from all dogs tested in Group 6 suggests that an ambient temperature of 5°C is not sufficient to elicit such a response from every animal. When changes in rectal temperature are plotted against different ambient temperatures, it is observed that the degree of cocaine-induced hypothermia (and hyperthermia) is directly proportional to ambient temperature (fig. 2). A similar effect has been observed with amphetamine in rats (Coper *et al.*, 1971). In that study, rats exhibited greater degrees of hypothermia at progressively lower ambient temperatures. The ambient temperature value at which amphetamine administration would produce zero change in body temperature was termed the specific indifferent temperature (*i.e.*, thermoneutral point) and was 22°C; the corresponding value for cocaine obtained in this study is 11.5°C (fig. 2).

Since hyperthermia was shown to be directly associated with death from cocaine, the aforementioned observations may prove to be of important clinical value. Even at this early stage of investigation, one could reasonably suggest that cocaine-intoxicated patients be kept in a cool environment and that attempts be made to reduce skin and core temperature.

Summary. This study has shown that hyperthermia is a very important factor in fatal cocaine intoxication. Chlorpromazine and pancuronium pretreatment effectively antagonized cocaine poisoning, whereas propranolol and pimozide administration were without effect. Furthermore, these experiments uncovered a hypothermic action of cocaine when infused at low ambient temperatures and demonstrated that hypothermia alone is sufficient to prevent mortality.

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