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# Acute Cocaine Toxicity: The Effect of Agents in Non-Seizure-Induced Death

CHUI-CHUNG TSENG,*[1] ROBERT W. DERLET† AND TIMOTHY E. ALBERTSON*†

**Department of Medical Pharmacology and Toxicology and †Division of Emergency Medicine and Clinical Toxicology, School of Medicine, University of California, Davis, Davis, CA 95616*

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TSENG, C.-C., R. W. DERLET AND T. E. ALBERTSON. *Acute cocaine toxicity: The effect of agents in non-seizure-induced death.* PHARMACOL BIOCHEM BEHAV **46**(1) 61–65, 1993.—Death from cocaine intoxication results from one or more of the multiple mechanisms including seizures, cardiovascular collapse, or apnea. In the free-moving rat model, continuous seizures are a major cause of brain. To study other mechanisms of brain unrelated to seizures in this model, we suppressed lethal seizures with diazepam (DZP) and investigated the effect of several pharmacological agents. Rats were pretreated with vehicle alone, diazepam 5 mg/kg alone, or a combination of DZP plus either nifedipine (NIFD) 2 mg/kg, propranolol (PROP) 10 mg/kg, or prazosin (PRAZ) 5 mg/kg. Five minutes after pretreatment, all animals received cocaine 100 mg/kg. Each test group consisted of 15 animals and all agents were given IP. Two animals in each group had cortical electrodes implanted. Animals that received vehicle followed by cocaine had 100% incidence of seizures and death. Those rats that received DZP alone followed by cocaine had no seizures and 53% death. Rats that received DZP plus NIFD or DZP plus PROP had suppression of seizures but no significant change in the incidence of death. The group that received DZP and PRAZ followed by cocaine had no seizures and 13% incidence of death ($p < 0.001$). Electroencephalogram recordings showed cortical electrical spike activity or spike-and-wave afterdischarges in all animals clinically observed to have seizures. In the absence of clinical seizure activity, no significant cortical spike activity was noted. It is concluded that animals protected from seizures with diazepam can still have nonseizure deaths after high-dose cocaine. The incidence of death in these animals is not reduced with nifedipine or propranolol pretreatment but is reduced with prazosin pretreatment.

Cocaine Diazepam Prazosin Seizures Respiratory arrest Death

COCAINE has multiple physiological effects and induces toxicity in animals and humans through more than one mechanism. Toxicity from seizures and status epilepticus have been described both in animal models and humans (3,6). Myocardial effects, including arrhythmias and myocardial depression, have also been described (12,18), although the precise etiology is unclear. Additionally, intense vasoconstriction, which can affect coronary arteries, cerebral arteries, and mesenteric and renal arteries, can result from cocaine toxicity (7). Some of the most severe clinical effects of cocaine such as myocardial infarction and cerebral vascular events have been attributed to its intense vasoconstrictive properties (2,15). More recently, attention has focused on cocaine-induced respiratory depression. In animals that receive a lethal dose of cocaine but are protected from seizures with an anticonvulsant, death appears to occur from a primary respiratory arrest (17,29,33,34). Death is prevented if the animal is placed on a ventilator at the time of its respiratory arrest.

In the rodent model, one of the first toxic effects of high-dose cocaine is seizures quickly followed by death. Death in these animals has been attributed to hypoxemia and acidosis induced by seizures (34). Because seizures appear to be the primary mechanism of cocaine toxicity in the rodent model, it would be expected that anticonvulsants could provide the greatest efficacy in the prevention of death. It is, therefore, difficult to study the effects of non-anti-convulsants in antagonizing the many other toxic effects of cocaine in this model unless seizures have been suppressed. In previous studies, agents that theoretically may protect against the cardiovascular toxic effects of cocaine, including propranolol, prazosin, and nifedipine, failed to protect rats from death (4,5). This may be because these compounds lack anticonvulsant properties and the seizure activity induced by cocaine results in death in this rodent model independent of any direct cardiovascular toxicity. Cocaine toxicity in humans appears to be more complicated than just the development of seizure activity. To extend the study of cocaine toxicity in the rodent model, animals were first treated with the anticonvulsant diazepam to prevent seizures and then a high toxic dose of cocaine was administered. Either nifedipine, propranolol, or prazosin was given

[1] Requests for reprints should be addressed to Robert W. Derlet, Division of Emergency Medicine and Clinical Toxicology, School of Medicine, University of California, Davis, Medical Center, Sacramento, CA 95817.

in combination with diazepam to determine if these pharmacological agents offered any additional protective effect against the nonconvulsant toxic effects of cocaine.

## METHOD

Male Sprague-Dawley rats weighing between 200 and 300 g were used in this experiment. The protocol was reviewed and approved by the UC, Davis Institutional Laboratory Animal Use and Care Committee. Animals were cared for following the guidelines of this committee. Rats were kept under 12 L : 12 D cycles and had ad lib access to food and water.

Animals were divided into five groups. Each group contained 15 animals. Two animals in each group underwent surgery for cortical electroencephalogram (EEG) implant as previously described (33,34). A Grass polygraph (Model 78D, Grass Instruments, Inc., Quincy, MA) was used to record cortical EEG. All agents were administered IP. Diazepam has previously been shown to have a dose-dependent protective effect against seizures induced by cocaine at 70 mg/kg IP, with significant protection at 2 mg/kg diazepam (3). Therefore, it was postulated that diazepam at 5 mg/kg would be able to completely suppress generalized seizure activity induced by 100 mg/kg cocaine HCl IP, which in pilot studies had been shown to produce 100% seizure and death in rats.

In the first group (controls), animals were pretreated with 1 ml/kg of the vehicle dimethyl sulfoxide (DMSO, Sigma Chemical Co., St. Louis, MO.) 5 min before challenge with 100 mg/kg cocaine HCl (Sigma) dissolved in normal saline (pH 5) at 50 mg/ml concentration. In the other four groups, animals were pretreated with either 5 mg/kg diazepam alone, 5 mg/kg diazepam plus 2 mg/kg nifedipine, 5 mg/kg diazepam plus 10 mg/kg propranolol, or 5 mg/kg diazepam plus 5 mg/kg prazosin followed by the same dose of cocaine 5 min later. The selected doses of all pretreatment agents had been tested for their nonlethality in pilot studies prior to the experiment.

Data were reported as overall percentages of generalized seizures and death for each group. Mean times to seizures and respiratory arrest were calculated to include SEM. The $\chi^2$ contingency test with Bonferroni adjustment was used to determine the overall statistical significance of the incidence of seizures and death in each group against all the other groups. The Student-Newman-Keuls test (multiple comparison procedures) was used to compare the statistical significance of the mean time to seizures and respiratory arrest in each group against all the other groups.

## RESULTS

The experimental protocols and results are summarized in Table 1. Representative EEG patterns from each group are illustrated in Fig. 1. Pilot animals tested with either 5 mg/kg diazepam, 5 mg/kg diazepam plus 2 mg/kg nifedipine, 5 mg/kg diazepam plus 10 mg/kg propranolol, or 5 mg/kg diazepam plus 5 mg/kg prazosin exhibited immobilization or drowsiness within 3 min. Respiration became slow and deep. All pilot animals survived.

### *Group 1: DMSO 1 ml/kg + Cocaine 100 mg/kg (Controls)*

This group had an incidence of generalized seizures of 100% (15/15) and death of 100% (15/15). The mean time to seizures and respiratory arrest (± SEM) was $2.9 \pm 0.4$ and $3.7 \pm 0.5$ min, respectively. In 8 of the 15 animals, the behavioral seizures started with a tonic-clonic activity and progressed to a tonic extension that was followed immediately by respiratory arrest and death. In the remaining animals, sudden respiratory arrest occurred after a short period of tonic-clonic activity in the absence of apparent tonic extensions. The behavioral seizures coincided with the EEG spike-bursts and spike-and-wave afterdischarges. The EEG tracings dropped to a flat line immediately following respiratory arrest.

### *Group 2: Diazepam 5 mg/kg + Cocaine 100 mg/kg*

There were no behavioral seizures and 53% (8/15) of the animals died ($p < 0.005$, compared to controls) in this group. The mean time to respiratory arrest was $9.4 \pm 1.1$ min, significantly ($p < 0.001$) increased compared to controls. Animals remained hypoactive after cocaine challenge. Respiration became slower with time. Respiratory arrest was the preterminal event by observation. EEG tracings exhibited occasional spike-wave complexes (SWCs) before respiratory arrest but no spike-bursts (SBs) or spike-and-wave afterdischarges were seen. A drop in the EEG amplitude was recorded seconds before respiratory arrest, followed by a complete flattening of the EEG tracing.

TABLE 1

INCIDENCE AND TIME TO COCAINE-INDUCED TOXIC EVENTS

| Group | *n* | Time to Seizures* | Incidence of Seizures (%) | Time to Respiratory Arrest* | Incidence of Death (%) |
|---|---|---|---|---|---|
| Vehicle + COC (Control) | 15 | 2 9 ± 0.4 (15) | 100 | 3.7 ± 0.5 (15) | 100 |
| DZP + COC | 15 | NA | 0† | 9.4 ± 0.5 (8)‡ | 53† |
| DZP + NIFD + COC | 15 | 5.6 (1) | 7† | 6.9 ± 0.4 (13) | 87 |
| DZP + PROP + COC | 15 | NA | 0† | 7 2 ± 0.8 (13) | 87 |
| DZP + PRAZ + COC | 15 | NA | 0† | 11.6 ± 6.5 (2)‡ | 13‡§ |

COC, cocaine (100 mg/kg); DZP, diazepam (5 mg/kg); NIFD, nifedipine (2 mg/kg); PROP, propranolol (10 mg/kg); PRAZ, prazosin (5 mg/kg); NA, not available.

*Data are shown as minutes ± SEM (number of animals)

†$p < 0.005$ compared to control group.

‡$p < 0.001$ compared to control group.

§$p < 0.025$ compared to DZP + COC group.

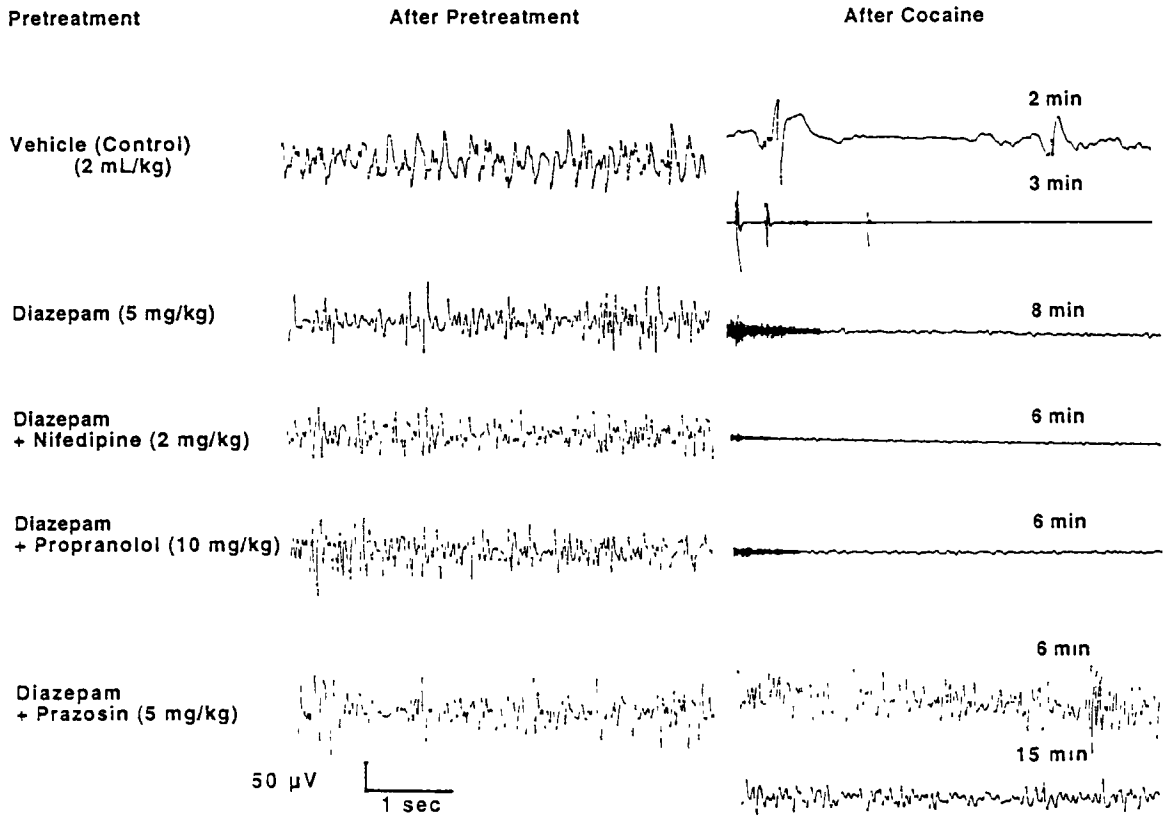


FIG. 1. Electroencephalogram (EEG) recordings obtained from rats pretreated with a variety of agents followed by 100 mg/kg cocaine IP. All animals appeared sedated prior to cocaine challenge except controls. The EEG recordings in the control animal showed continuous spike-bursts and spike-and-wave afterdischarges in coincidence with overt seizure activity until respiratory arrest, which was followed quickly by a flat EEG and death. Animals pretreated with diazepam in combination with nifedipine or propranolol had no overt or electrical seizure activity after cocaine challenge but manifested respiratory arrest followed by EEG flattening and death. The animal pretreated with diazepam plus prazosin failed to demonstrate seizure activity and survived cocaine challenge

*Group 3: Diazepam 5 mg/kg + Nifedipine 2 mg/kg + Cocaine 100 mg/kg*

The incidence of behavioral seizures and death was 7% (1/15) and 87% (13/15), respectively. The former was significantly ($p < 0.004$) reduced when compared to controls. The mean time to respiratory arrest was $6.9 \pm 0.4$ min, significantly ($p < 0.001$) increased compared to controls but decreased compared to Group 2. Animals became agitated after cocaine challenge. Respiratory arrest was also the preterminal event by observation. There were a few more SWCs recorded prior to respiratory arrest. Only the animal that developed overt seizures showed a continuum of SBs before respiratory arrest, which was followed by a few more SBs but no spike-and-wave afterdischarges prior to the development of a flat EEG recording.

*Group 4: Diazepam 5 mg/kg + Propranolol 10 mg/kg + Cocaine 100 mg/kg*

No behavioral seizures were noted. Death occurred in 87% (13/15) of the animals. The mean time to respiratory arrest was $7.2 \pm 0.8$ min. Animals also became agitated and relatively hyperactive after cocaine challenge. Respiratory arrest was also observed to be the preterminal event. The EEG changes were similar to those seen in Group 2.

*Group 5: Diazepam 5 mg/kg + Prazosin 5 mg/kg + Cocaine 100 mg/kg*

No behavioral seizures were seen. Only 13% (2/15) of the animals died ($p < 0.001$, compared to controls). Additionally, the incidence of death was significantly ($p < 0.025$) lower than that of diazepam alone (Group 2). Animals were observed to remain hypoactive after cocaine challenge. This contrasted with the relative hyperactivity seen in animals pretreated with diazepam plus nifedipine or propranolol (Group 3 or 4). Respiratory rates appeared to increase compared to before cocaine challenge and remained rapid for hours, suggesting that this drug combination may have a protective effect against respiratory depression. This also contrasted with Group 2, in which the respiratory rate decreased with time until respiratory arrest. The mean time to respiratory arrest in the two deceased animals was $11.6 \pm 6.5$ min, substantially ($p < 0.001$) prolonged compared to the control group. Both animals with EEG recordings in this group survived. Only occasional spike-wave complexes were recorded.

## DISCUSSION

In this study, cocaine-induced seizure activity was eliminated as a cause of death by diazepam pretreatment. Cocaine-induced death occurred through other mechanisms such as

primary respiratory arrest or direct cardiac toxicity. Diazepam has been shown previously to prevent seizure-induced death from lower toxic doses of cocaine in rats (3). In this study, diazepam (5 mg/kg) alone was able to effectively suppress seizures but only partially reduced the incidence of death induced by a lethal high dose of cocaine (100 mg/kg, IP). The effectiveness of prazosin (5 mg/kg), in combination with diazepam, in preventing death from high-dose cocaine toxicity was demonstrated in this model. When combined with diazepam, both nifedipine and propranolol failed to decrease the incidence of death and shortened the time to respiratory arrest as compared to diazepam pretreatment alone, suggesting that they add little to reduce seizure-protected cocaine toxicity in this model.

Prazosin, an $\alpha_1$-adrenoceptor antagonist, but not propranolol and nifedipine, at the tested dose was able to prevent high-dose cocaine-induced death in seizure-suppressed animals. This suggests that $\alpha_1$-adrenergic mechanism may be involved in the pathogenesis of cocaine-induced toxicity, presumably related to the cardiotoxic effects of cocaine potentiated by the previously demonstrated acute hypoxia and acidosis from respiratory depression (34). This postulation is partially supported by reports using cardiac tissue models that $\alpha_1$-adrenergic blockade can prevent the metabolic and mechanical abnormalities associated with acute hypoxia, including depletion of myocardial high-energy phosphates, release of adenosine triphosphate (ATP) metabolites and creatinine kinase from the myocardium, and increases in tissue calcium content (19,26–28). Additionally, the $\alpha_1$-adrenergic blocking effect of prazosin may reverse the cardiovascular effects of cocaine by dilating the coronary arteries (14) and reducing the systemic vascular resistance and blood pressure elevations. The resulting enhancement of myocardial oxygen supply as well as oxygen demand reduction may reduce the myocardial depressive action of hypoxia and acidosis seen with cocaine-induced respiratory depression. The diazepam/prazosin combination may also antagonize cocaine toxicity by enhancing respiratory drive, in contrast to the respiratory depression (slowing of respiration) observed in the other combination groups. The mechanism for such a possible respiratory-enhancing effect is not clear, but it may be the result of a nonspecific effect of prazosin (27). A similar respiratory-enhancing effect has been demonstrated in anesthetized rats pretreated with phentolamine followed by IV infusion of cocaine (17). It is reported that phentolamine can prevent cocaine-induced respiratory depression by increasing respiratory rate and tidal volume (17).

Reports on the protective effect of $\alpha$-adrenergic blockers against cocaine toxicity are limited. Phentolamine, a nonselective $\alpha$-adrenergic antagonist, has been used in the treatment of hypertensive emergencies and cocaine-induced myocardial ischemia with presumed effectiveness in humans (10). Coronary vasoconstriction induced by intranasal cocaine was shown to be reversed by intracoronary infusion of phentolamine in a controlled human study (14). The antagonistic effect of prazosin against cocaine has been demonstrated in pigeons and monkeys using behavioral measures, including locomotor activity (24) and operant responding (29). Phentalomine can attenuate cocaine-induced pressor response in rats via a peripheral $\alpha$-adrenergic mechanism (11). Prazosin, but not phentolamine, has previously been shown to significantly protect against cocaine-induced death but not seizures in rodents (5). In another rodent model, both prazosin and phentolamine were reported to partially protect against cocaine toxicity (32).

The protective effect of $\beta$-adrenergic antagonists against cocaine toxicity is controversial. Propranolol has been used clinically as an antidote for some cardiovascular effects of moderate cocaine toxicity, including tachycardia, tachypnea, and hypertension (20,21). Propranolol pretreatment was reported to improve survival in mice after a lethal dose of IV cocaine (22). Propranolol has also been demonstrated to provide a dose-dependent protection against a lower toxic dose of cocaine in rats (5). However, in the current study with a dose that had been previously shown to be effective in preventing cocaine-induced death (5) propranolol in combination with the anticonvulsant diazepam was ineffective in protecting against a higher dose of cocaine. Although various doses of propranolol or a longer time before cocaine challenge may have different effects, other reports also demonstrated the ineffectiveness of propranolol in the prevention of cocaine lethality in different animals species, including rats (32), dogs (1), and monkeys (8). Propranolol has also been shown to potentiate cocaine-induced respiratory depression in anesthetized rats (17). Many of these studies suggested that severe CNS and cardiovascular toxicity such as seizures, respiratory depression, and coronary vasoconstriction might be actually potentiated by propranolol pretreatment. Similarly, cocaine-induced coronary vasoconstriction has also been shown to be potentiated by propranolol in isolated procine coronary ring segments (35) and by intracoronary infusion of propranolol in humans (13), probably due to the unopposed $\alpha$-adrenergic activity.

A number of calcium channel blockers have been studied for their potential protective effect against cocaine-induced toxicity and death. Nitrendipine, when infused intraarterially, has been reported to be an effective antidote to cocaine toxicity in restrained, conscious rats by increasing the survival time and the lethal dose of cocaine required when infused simultaneously through an intraarterial route (30) or by preventing death from a lethal dose of IP cocaine (32). It has also been shown that pretreatment with the calcium channel blockers flunarizine, diltiazem, and nicardipine, but not with verapamil, significantly prevents cocaine-induced seizures and death (32). However, many of the calcium channel blockers previously tested in this laboratory, including nifedipine, verapamil, and diltiazem, failed to demonstrate protection against cocaine-induced seizures and death in rats (4).

Nifedipine, by virtue of an antagonism of calcium influx through the slow channel on the cell membrane, has potent coronary and peripheral arterial dilator properties with concomitant improvements in oxygen supply/demand and reductions in peripheral vascular resistance (25). In human volunteers, nifedipine pretreatment attenuated some subjective effects of cocaine, including scores on the General Drug Effect and Tension/Anxiety and Confusion/Bewilderment scales (16). In rats, nifedipine has been shown to have no effect on the cocaine-enhanced locomotor activity such as the increased frequency of rearings and ambulations (23) while in anesthetized dogs nifedipine pretreatment can protect against, but not reverse, cocaine-induced myocardial depression and coronary blood flow decrease (9). Because nifedipine and prazosin are both vasodilators, it is intriguing to speculate why prazosin offered additional protection but nifedipine failed to protect against cocaine toxicity. The negative inotropic effect of the nifedipine, a property not seen with prazosin, may be accentuated by the cocaine-induced myocardial depression. In addition, prazosin may have a nonspecific respiratory-enhancing effect not seen with nifedipine when combined with diazepam. The CNS action of prazosin that is not shared by nifedapine

may also be important in antagonizing cocaine-induced seizures, respiratory depression, and lethality. Although various doses of nifedipine or a longer time before cocaine challenge would have to be tested in combination with diazepam before completely ruling out a protective effect with nifedipine, it appears unlikely that nifedipine offers any additional protection against cocaine-induced toxicity in the seizure-suppressed rat model.

In conclusion, rats protected from seizures by a high dose of diazepam have nonseizure deaths after a high lethal dose of cocaine. This diazepam dose, when combined with a high dose of nifedipine or propranolol, continued to only protect against cocaine-induced seizures but not death. Diazepam in combination with prazosin at the tested dose was found to be effective in antagonizing high-dose cocaine toxicity including seizures and death.

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