Highlight Article: 2003 ACMT/McNeil Fellows-in-Training Research Grant Award Winner

The Effect of Amiodarone Pretreatment on Survival of Mice with Cocaine Toxicity

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ABSTRACT

Introduction: Cocaine is a common drug of abuse and use has been associated with ventricular dysrhythmias. Published guidelines suggest that amiodarone is the first line antidysrhythmic for ventricular tachycardia and fibrillation. However, the effects amiodarone in the setting of cocaine toxicity are unknown and unstudied. The purpose of this study was to evaluate the safety and efficacy of amiodarone pretreatment in a murine model of acute cocaine toxicity.

Methods: This was a randomized, blinded, placebo controlled investigation using male CF-1 mice weighing 29–37 g. First, the safety of an intraperitoneal dose of amiodarone (40 mg/kg) was confirmed in 5 mice. Second, based on preliminary investigations, an approximate intraperitoneal LD₅₀ dose of cocaine (110 mg/kg) was identified and used as the cocaine dose in this study. Animals were then randomized to 2 groups. The control group received 0.5 mL of intraperitoneal 0.9% saline 30 minutes before cocaine. The study group received 40 mg/kg of intraperitoneal amiodarone (40 mg/kg) 30 minutes before cocaine. A blinded observer monitored mice for 2 hours after cocaine administration.

Results: No mice in the amiodarone-only group developed any signs of toxicity or died. In the saline + cocaine group 31/32 (96.9%; 95% CI 83.8 to 99.9) mice seized with a median time to seizure of 2.5 minutes, and 23/32 (71.9%; 95% CI 52.3 to 86.3) died with a median time to death of 5.5 minutes. In the amiodarone + cocaine group 31/33 (93.9%; 95% CI 79.0 to 99.3) mice seized with a median time to seizure of 2.0 minutes, and 24/33 (72.7%; 95% CI 54.5 to 86.7) died with a median time to death of 6.0 minutes. All animals that died did so within 9 minutes. The difference in the proportion of animals dying in the amiodarone + cocaine group compared to the saline + cocaine group was 0.008 (–21 to 22%).

Conclusions: In this study, pretreatment with amiodarone in cocaine poisoned mice resulted in no change in seizure incidence or mortality. However, definite conclusions about the reason for these findings cannot be drawn from this model.

Keywords: cocaine, toxicity, amiodarone, mouse

Financial Disclosures: This project was supported by the American College of Medical Toxicology/McNeil Fellows in Training Grant (C. DeWitt), the Hartford Foundation Jahnigen Career Scholars Award (K. Heard), and a Department of Health and Human Services, National Institutes of Health (N. Cleveland; grant # 5 T35 DK007496-18).

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INTRODUCTION

In the United States, cocaine is a commonly abused drug, and cocaine use is the most frequent cause of drug related visits to emergency departments [1]. Numerous acute medical problems have been associated with cocaine abuse, including cardiac dysrhythmias [2–7]. Although the etiology of cocaine-associated dysrhythmias is complex and not fully understood, lethal ventricular dysrhythmias are a theorized cause of sudden death associated with cocaine use [8]. Ventricular dysrhythmias that rapidly develop after cocaine use are thought to be due to the local anesthetic effects of cocaine [9]. The dysrhythmias may be due to alterations in automaticity, autonomic dysregulation, ischemia, and potentiation of reentrant dysrhythmias [10]. Although ventricular dysrhythmias are infrequently reported with cocaine use, they may account for a significant number of cocaine-associated deaths, particularly in the pre-hospital setting.

Current drug therapy guidelines for resistant or hemodynamically stable ventricular tachycardia (VT) or ventricular fibrillation (VF) associated with cocaine are sodium bicarbonate followed by lidocaine [11]. However, in the “Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care”, amiodarone is the first line antidysrhythmic for VT and VF [12]. Because of the recommendations for amiodarone, the fact that cocaine is a common drug of abuse, and difficulty in rapidly differentiating cocaine-associated dysrhythmias from other causes, it is inevitable that amiodarone will be given to a cocaine-poisoned patient. It is important that we understand how medications used to treat dysrhythmias may affect cocaine poisoned patients, but the effects of amiodarone on cocaine toxicity are unknown.

In vitro and *in vivo* studies demonstrate the effect of cocaine on myocardial sodium channels [13,14]. The effects are similar to those seen with class Ia and Ic antidysrhythmics [9]. Other *in vitro* studies indicate that cocaine blocks delayed rectifier potassium channels [15] and, in high concentrations, decreases inotropy presumably by decreasing calcium influx [10]. Cocaine intoxication increases central sympathetic drive and circulating catecholamines [16].

Amiodarone is a class III antidysrhythmic drug that primarily affects delayed rectifier potassium currents during phase 3 of depolarization [17]. Amiodarone also blocks sodium channels similar to Ib antidysrhythmics, [18] blocks slow inward calcium currents, [17] and noncompetitively antagonizes α and β -adrenergic receptors [19,20]. Theoretically, amiodarone and cocaine could produce synergistic blocking of potassium and calcium channels leading to cardiovascular dysfunction and dysrhythmias. Conversely, the sympatholytic effects of amiodarone could be of great benefit in the setting of cocaine toxicity. Based on previous murine models, the addition of a second sodium channel antagonist could improve survival in cocaine poisoning [21,22]. Amiodarone is not known to cause agitated delirium or seizures, [23] and therefore it would not be expected to potentiate the effects of cocaine on the central nervous system.

The purpose of this study was to evaluate the safety and efficacy of amiodarone pretreatment in a murine model of acute severe cocaine toxicity. We concluded that the sympatholytic and sodium channel effects of amiodarone would outweigh the potential detrimental effects of calcium and potassium channel blockade. We hypothesize that amiodarone would increase survival, but not alter the incidence of seizures. An initial power calculation yielded a sample size of 90 animals per group with 80% power ($\alpha = 0.05$) to detect a 20% increase in survival in amiodarone treated animals.

MATERIALS AND METHODS

The study was a randomized, blinded, placebo controlled investigation approved by our animal care committee. Male CF-1 mice (Charles River Laboratories, Willmington, MA) weighing 29–37 g were used. Local animal care guidelines were used. Animals were housed 5 to a cage, with 16/8 hour dark-light cycles, allowed *ad libitum* access to a standard diet and water, and allowed to acclimatize 5 days before experimentation. All animals were immediately weighed before drug administration, and each animal participated in only one trial. All drugs were administered via intraperitoneal (IP) injection. Cocaine hydrochloride (Sigma Chemical Co., St. Louis, MO) and pharmaceutical amiodarone (50 mg/ml amiodarone hydrochloride, 100 mg/ml polysorbate 80, 20.2 mg/ml benzyl alcohol, Wyeth-Ayerst, Collegeville, PA) were diluted in 0.9% saline to create injection volumes of approximately 0.5 ml for amiodarone injections and approximately 0.5 ml (in order to administer 110 mg/kg) for cocaine. Each diluted 0.5 ml injection of amiodarone contained 0.45 ml of 0.9% saline and 0.05 ml of pharmaceutical amiodarone. Placebo treated animals received 0.5 ml of 0.9% normal saline. A 0.5 ml injection of diluted amiodarone provided approximately 2.3 mEq/kg of sodium, and a 0.5 ml of 0.9% saline provided approximately 2.6 mEq/kg of sodium.

A preliminary study was performed to identify an approximate LD_{50} dose of cocaine. Previous murine studies obtained LD_{50} doses of IP cocaine of approximately 95 mg/kg [24,25,21,26]. The dose lethality curve for cocaine is sigmoidal and very steep near the LD_{50} [21]. Obtaining an exact LD_{50} would require a large number of mice. Therefore, groups of 7 animals were given escalating doses of cocaine (95, 105, and 110 mg/kg). Ninety-five, 105, and 110 mg/kg resulted in animal deaths of 1/8, 3/7, and 3/7 respectively. One hundred-fifteen mg/kg resulted in 100% lethality when administered to 3 animals. Because we employed a control group and looked for a 20% difference in survival, we only needed to approximate an LD_{50} . A 110 mg/kg of cocaine hydrochloride with strict weight-based dosing was used in the remainder of the study.

The antidysrhythmic dose of amiodarone in mice is unknown. The only identified murine study involving amiodarone used an IP dose of 50 mg/kg [27]. Rat experiments of dysrhythmia treatment have used IP doses ranging from 5 to 50 mg/kg [28,29]. We estimated that 40 mg/kg of amiodarone is

Figure 1. Study Algorithm.

approximately equal, on a mg/body surface area basis, to the cardiac arrest dose of amiodarone for a 70 kg human [12]. A dose of 40 mg/kg was used in this study. The safety of this dose was confirmed prior to the study by administering amiodarone to 5 mice.

Animals were assigned to either amiodarone or placebo arms using a random number generator. Animals received either NS or amiodarone 30 minutes prior to cocaine administration. After cocaine administration, mice were placed in a clear glass cage and monitored by a blinded observer for 120 minutes (*See Figure 1*). The following were recorded at the time of occurrence: death or moribund state, seizure, time to death, and time to first seizure. Seizure was defined as an obvious tonic and/or clonic activity or loss of the righting reflex. Moribund animals (defined by a cessation of respirations for 30 seconds, seizures lasting at least three minutes, or eyes becoming darker than the typical red color) were considered dead and euthanized. All animals alive at 120 minutes were counted as survivors.

RESULTS

None of the 5 mice receiving amiodarone only developed signs of toxicity or died. All animals alive at 120 minutes appeared well. The mortality rate increased following cocaine administration. The results for animal weights, seizures, time to seizure, death, and time to death in the placebo and amiodarone arms are

TABLE 1. Comparative data in placebo and amiodarone-treated experimental groups

Group (Number per group)	Cocaine + 0.9% saline (32 animals)	Cocaine + Amiodarone (33 animals)
Mean weight in grams (95% CI)	32.5 (31.8–33.1)	32.8 (32.0–33.5)
Range of weight in grams	29–37.5	29–37
Number with seizure (percent and 95% CI) [†]	31/32 (96.9%, 83.8 to 99.9%)	31/33 (93.9%, 79.0 to 99.3%)
Range of time to seizure (minutes)	1–3.5	1.5–17
Median time to seizure (minutes)	2.5	2.0
Number of deaths (percent and 95% CI) [‡]	23/32 (71.9%, 52.3 to 86.3%)	24/33 (72.7%, 54.5 to 86.7%)
Range of time to death (minutes)	3–8.5	3–9
Median time to death (minutes)	5.5	6.0

[†] The difference in the proportion of animals that had seizures in the amiodarone arm vs. the placebo arm was -0.03 (unable to calculate 95% confidence interval due to the small number of seizure-free mice).

[‡] The difference in the proportion of animals dying in the amiodarone arm vs. the placebo arm was 0.008 (-21 to 22%).

shown in Table 1 and the survival curve in Figure 2. The difference in the proportion of animal deaths in the amiodarone arm vs. the placebo arm was 0.008 (-21 to 22%). The difference in the proportion of animals that had seizures in the amiodarone arm vs the placebo arm was -0.03 (We were unable to calculate 95% confidence interval due to the small number of seizure-free mice). An interim power analysis showed less than a 5% chance of finding a survival benefit $>22\%$ in the amiodarone group.

DISCUSSION

In this model of acute cocaine toxicity, amiodarone had no effect on seizures or mortality. In order to understand the potential interactions of amiodarone and cocaine the cardiovascular effects of each drug must be considered.

Cocaine

Similar to the complex cardiovascular effects of cocaine, the pathophysiology of death related to cocaine is complex and only partially understood. It has been proposed that sudden cocaine-related death may be due to the development of agitated delirium and central dopamine effects [14,30]. The sudden death related to cocaine use may be due to cardiac etiologies [31]. Nearly every type of dysrhythmia has been reported with

Figure 2. Survival Curve for amiodarone + cocaine vs. 0.9% saline + cocaine.

cocaine use, [4] and it stands to reason that sudden death related to cocaine could be due to lethal dysrhythmias. Ventricular dysrhythmias are a well-recognized complication of myocardial infarction, and ventricular dysrhythmias certainly occur in the setting of cocaine-induced myocardial ischemia [32]. However cocaine induced ventricular dysrhythmias unrelated to myocardial ischemia are thought to occur [3,31]. Aside from cocaine-induced myocardial ischemia as a cause for ventricular dysrhythmias, the dysrhythmogenic potential of cocaine is not clearly defined. This is probably due to several factors; including cocaine's multiple dose dependent electrophysiological effects, [33] cocaine-induced metabolic derangements, [34] environmental factors, [35] sex, [36] genetic differences, [37] and structural myocardial changes related to chronic cocaine use [31]. Human electrophysiological data related to cocaine is limited; [38] and because of obvious reasons, information on the effects of large doses does not exist. Much of the data on cocaine's electrophysiologic effects is based on animal studies, and interpretation can be difficult because of differing experimental designs and the separation of electrophysiologic effects from sympathetic effects in *in vitro* models.

The local anesthetic effects of cocaine are due to its ability to block fast sodium channels. This local anesthetic effect extends to cardiac tissue where cocaine causes Class Ia or Ic antidysrhythmic effects in a dose dependent manner [9,13,39,40]. Cocaine causes a rate-dependent sodium channel blockade, [16,31,41] and the sodium channel effects are increased as the sympathomimetic effects of cocaine increase heart rate. Wide complex dysrhythmias related to cocaine-induced sodium channel blockade, although rare, are reported [3].

Another potential dysrhythmogenic property of cocaine is its ability to block potassium channels [15,39]. Cocaine appears to

interfere with the delayed rectifier potassium current by blocking the HERG channel [42,43]. Blockade of this channel sets the stage for early afterdepolarizations that leads to QT prolongation and dysrhythmias [44]. Torsade de pointes has been associated with cocaine use [41,45]. However, these authors concluded that cocaine only use contributed to an underlying congenital long QT syndrome in these patients. The overall contribution of cocaine-induced potassium channel blockade in the generation of ventricular dysrhythmias is unclear. It has been suggested that cocaine's effect on potassium channels may display a reverse use-dependence such that blockade would decrease as heart rate increases [41]. The sodium channel blockade seen at higher heart rates and higher cocaine concentrations may offset the effects of potassium channel blockade [41]. This biphasic effect of potassium channel blockade has been observed for Class Ia antidysrhythmics [46,47]. Thus, cocaine may produce qualitatively different effects on potassium channels and repolarization depending on the dose (i.e., recreational use versus overdose) [48]. If these theories are true, the high doses of cocaine used in our model would have a negligible effect on myocardial potassium currents.

The sympathomimetic effects of cocaine may also be responsible for dysrhythmogenesis. Sympathetic stimulation of cardiac beta-receptors leads to increased intra-cellular calcium levels [10]. Elevated intra-sarcolemmal calcium levels appear to be the basis of delayed afterdepolarizations [44]. Increased intra-cellular calcium causes the cell to become relatively more depolarized, moving the membrane potential closer to the depolarization threshold leading to spontaneous myocardial depolarization and dysrhythmias [44]. Although *in vitro* models suggest that high concentrations of cocaine can decrease L-type calcium currents [15] and intra-cellular calcium levels (possibly via sodium

channel blockade) [49] they may be overridden by sympathetic effects in an *in vivo* setting.

Amiodarone

Although amiodarone is considered a Class III antidysrhythmic, it has multiple and only partially understood cardiovascular effects that span all Vaughn Williams classes. It is important to note that amiodarone has distinctly different effects when administered chronically as opposed to acute intravenous administration [18,50,51]. For this study, only acute effects are applicable. Amiodarone acutely blocks delayed rectifier potassium channels, and this appears to be due to the effects on the HERG channel [52,53]. Amiodarone also acutely blocks fast sodium channels similar to lidocaine [54] and blocks slow inward calcium currents [18,55]. Blockade of potassium, sodium, and calcium currents appears to be both use dependent and voltage dependent. The effects increase with increasing frequency of depolarization when the cell is relatively more depolarized [18,53,55]. Amiodarone also possesses sympatholytic effects similar to both α and β antagonists. However, amiodarone's adrenergic antagonism appears to be unrelated to competitive receptor blockade, a mechanism distinctly different from α and β blockers [19,20].

The commercial diluent (polysorbate 80) may have cardiovascular effects that could contribute to the effects of intravenous amiodarone, [56–58] but these effects are short-lived and would likely have no or minimal effects by the time cocaine was administered. The animals in our study received 80 mg/kg of polysorbate 80, but in another mouse study a dose of 100 mg/kg had no observable effect [59]. Intravenous amiodarone also contains 20.2 mg/ml of benzyl alcohol. Animals in our study received 16.2 mg/kg of benzyl alcohol, a dose significantly less than that observed to produce toxicity in mice [60].

Cocaine and Amiodarone

The complexity of the physiologic actions of these two drugs underlies the difficulty in drawing conclusions as to why amiodarone had no effect on survival. Varied cardiovascular effects of amiodarone could potentially increase or decrease mortality in acute severe cocaine poisoning. However, the combination of cardiovascular effects of amiodarone may negate each other when high-dose cocaine is administered. Amiodarone's sodium channel effects may attenuate cocaine-induced sodium channel blockade. Administration of a drug with effects similar to lidocaine may appear counterintuitive in the setting of cocaine poisoning. Animal models have shown improved survival when a second fast sodium channel-blocking agent is administered to cocaine-poisoned mice [21,22]. The benefit of adding a second sodium channel-blocking agent may lie in the drug displacing cocaine from sodium channels. This effect was demonstrated in *in vitro* studies with lidocaine, [61–63] but the combination of lidocaine and cocaine also increased the incidence of seizures in animal models [21,64] and increased the incidence of seizures and death in a rat model [65]. Amiodarone did not alter survival in a mouse model of tricyclic antidepressant poisoning [66].

The sympatholytic effects of amiodarone could be of potential benefit in cocaine toxicity. It is unclear if there is a relative difference in amiodarone's ability to block α or β adrenergic responses. This may be of potential concern because of the possibility of unopposed alpha effects with cocaine administration. In animal models amiodarone decreases the hypertensive response to epinephrine and norepinephrine [20,67]. It may be argued that amiodarone (via β -antagonistic effects) would slow the heart rate, allowing cocaine (because of reverse use-dependence) to produce more potassium channel blockade. Yet, amiodarone is believed to have use-dependent potassium channel effects, which would be offset by slowing the heart rate. Slowing of the heart rate would decrease the sodium channel blocking effects of cocaine and the sodium and calcium channel blocking effects of amiodarone. By decreasing sympathetic effects of cocaine, amiodarone could also decrease intra sarcolemmal calcium levels. Doses of cocaine used in this model may be high enough to decrease myocardial calcium influxes. Thus contractility may be decreased by cocaine-induced limitation of calcium influx (when the sympathetic response is blunted) and potentially by amiodarone's effect on calcium influx. Decreased intracellular calcium levels and contractility may be a reason calcium channel blockers appear to increase the lethal effects of high dose cocaine [59,68].

LIMITATIONS

Several limitations of this study warrant comment. Without invasive monitoring, the cardiovascular and electrophysiologic effects of amiodarone and cocaine cannot be confirmed. In addition, the exact cause of death is unclear from this model. It is possible that death was due to non-cardiac causes.

Although it seems unlikely, we cannot conclude that the additional 0.3 mEq/kg of sodium administered to control animals (from saline injection) provided a degree of protection from cocaine to the extent that we were unable to measure a potential beneficial effect of amiodarone.

There may also be species differences in responses to cocaine and amiodarone. Although, studies have demonstrated the ability of murine hearts to fibrillate, [69–71] there may be differences in the fibrillation propensity in mice and humans with cocaine poisoning. We were able to identify one study where amiodarone was administered to mice [27](for aconite poisoning), and we cannot be certain that amiodarone possesses the same antidysrhythmic effects in mice as it does in humans.

Finally, the pretreatment design may not extend to the clinically relevant context of amiodarone administration after cocaine use. Extending these results to a clinical setting should be done cautiously.

CONCLUSION

Pretreatment with amiodarone in acute severe cocaine poisoning did not affect seizure incidence or mortality. Definite

conclusions as to the reason for these findings cannot be drawn from this model. It is important to mention that amiodarone did not increase the incidence of mortality or seizure. Additional studies utilizing hemodynamic and electrocardiographic monitoring are required to conclude that current antidysrhythmic guidelines for amiodarone administration in VT/VF are safe for cocaine intoxicated patients.

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