Cardiovascular Pharmacology

PM101: A cyclodextrin-based intravenous formulation of amiodarone devoid of adverse hemodynamic effects

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ABSTRACT

Intravenous amiodarone (Amiodarone IV) is widely used to treat cardiac arrhythmias. The most frequent clinical adverse event associated with Amiodarone IV administration is systemic hypotension which has been attributed to the cosolvents used in the formulation, polysorbate 80 and benzyl alcohol. To minimize hypotension Amiodarone IV is diluted in 5% dextrose in water prior to administration and slowly infused. PM101 is a novel intravenous formulation that uses sulfobutylether-7-beta-cyclodextrin to solubilize amiodarone, and thus should be devoid of the untoward hemodynamic effects associated with polysorbate 80 and benzyl alcohol. Beagle dogs ($n = 7$/group) were anesthetized with morphine and α-chloralose and instrumented to assess aortic blood pressure, cardiac output, cardiac contractility, and heart rate. Animals were treated with the U.S. approved human-equivalent loading dose (2.14 mg/kg) of Amiodarone IV, PM101, and their respective vehicle controls. Administration of Amiodarone IV rapidly and significantly decreased mean aortic pressure, cardiac output, and cardiac contractility. A significant increase in heart rate was also observed as was a transient, but not significant, decrease in systemic vascular resistance. A similar pattern of rapid and significant hemodynamic changes was produced by the Amiodarone IV Vehicle (polysorbate 80/benzyl alcohol) alone. In marked contrast, PM101 and its vehicle produced no significant hemodynamic effects. This study provides a useful model for the continued search for a safe and effective intravenous amiodarone formulation devoid of the hypotensive risk associated with the current commercial formulation.

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1. Introduction

Intravenous amiodarone is commonly and successfully used to treat atrial and ventricular cardiac arrhythmias (Helmy et al., 1988; Scheinman et al., 1995; Desai et al., 1997; Kudenchuk, 1999), although hemodynamic changes are known to occur with its clinical use. In clinical trials, hypotension was common following dosing, occurring in 15% to 26% of patients treated (Kosinski et al., 1984; Kowey et al., 1995; Scheinman et al., 1995; Levine et al., 1996). In patients with ventricular arrhythmias, the hypotension was clinically important and required intervention, often in the form of pressor therapy (Kowey et al., 1995; Levine et al., 1996). Deaths from complications of hypotension have been reported (Levine et al., 1996).

Intravenous amiodarone-induced hypotension is thought to be related to non-amiodarone constituents of its formulation, which include polysorbate 80 and benzyl alcohol as solubilizing agents. The hypotensive liability of polysorbate 80 was evident in its initial animal testing (Krantz et al., 1948) and has been confirmed in subsequent investigations (Gough et al., 1982; Platou and Refsum, 1986). Benzyl alcohol may also contribute to a hypotensive response because of its negative inotropic effects (Yasaka et al., 1979).

The current U.S. labeling of the commercial formulation of intravenous amiodarone has a warning about its potential to cause hypotension and stipulates that the loading dose of 150 mg (or 2.14 mg/kg assuming a 70-kg patient) should be diluted 33-fold in 5% dextrose in water for injection and infused over 10 min to minimize this risk (Abraxis Pharmaceutical Products, 2008). More rapid administration (e.g. bolus push) would be advantageous in the treatment of life-threatening ventricular arrhythmias. Efforts to minimize these hemodynamic effects have focused on the development of alternative formulations of amiodarone, including an emulsion with tocopherol (Kessler et al., 2002), a suspension of amiodarone in 0.1 M acetate buffer

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at pH 3.8 (Somberg et al., 2002; Somberg et al., 2004a; Somberg et al., 2004b; Somberg et al., 2005), a suspension of amiodarone in lactate buffer (Kipp et al., 2002), and amiodarone solubilized in methoxy poly (ethylene oxide)-*block*-poly(ester) micelles (Elhasi et al., 2007). None of these approaches has yet resulted in an approved product.

Cyclodextrins are commonly used in the pharmaceutical industry as complexing agents that increase the water solubility, bioavailability, and stability of poorly soluble drugs (Loftsson et al., 2005). PM101 is an intravenous formulation of amiodarone using sulfobutylether-7-beta-cyclodextrin (SBE7betaCD, Captisol®, Cydex Pharmaceuticals, Inc., Lenexa, KS) in an effort to provide a stable agent that can be rapidly administered intravenously without the risk of hypotensive adverse events. The current study tested the hypothesis that the PM101 formulation of amiodarone was devoid of hypotension when administered as a bolus push injection. Here we describe the hemodynamic responses to PM101 and compare them to the commercial formulation of intravenous amiodarone.

2. Materials and methods

2.1. Ethics

All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996). The protocols were reviewed and approved by the Institutional Animal Care and Use Committee of CorDynamics (Chicago, IL), where the studies were performed.

2.2. Animals

Female beagle dogs between 7 and 11 months of age (6 to 12 kg) were obtained from Covance Research Products (Kalamazoo, MI). The dogs were housed in pens and kept on a 12 h light/dark cycle. Each dog received 215 g/day of a 25% protein diet and each had free access to water. Female dogs were used because of their increased proclivity for prolonged ventricular repolarization (i.e., long QT interval) in the presence of human ether-a-go-go related gene (hERG) antagonists compared to males (i.e. class III antiarrhythmic agents; Wolbrette, 2002; Hondeghem et al., 2003).

2.3. Surgical procedures

After an overnight fast, morphine (1 mg/kg, s.c.) was administered and dogs were anesthetized with α-chloralose (120 mg/kg, i.v.). Anesthesia was maintained by a constant infusion of α-chloralose (35 to 75 mg/kg/h, i.v.) through an indwelling catheter in the saphenous or cephalic vein. This catheter was also used for test drug administration. Each dog was intubated and ventilated with room air supplemented with oxygen to maintain blood gases within normal ranges. A Swan-Ganz thermodilution catheter was advanced through the jugular vein into the right atrium and secured in the capillary wedge position for measurement of cardiac output. A solid-state, high-fidelity pressure monitoring catheter (Millar Instruments, Inc., Houston, TX) was advanced through the carotid artery into the left ventricle for measuring left ventricular and aortic pressures. Electrocardiograms and hemodynamic parameters were continuously monitored and recorded with a Notocord HEM data capture system (v4.1.0.45, Croissy sur Seine, France). At the conclusion of each experiment, dogs were euthanized by barbiturate overdose while anesthetized.

2.4. Study drugs

The commercial formulation of intravenous amiodarone (Amiodarone IV) was obtained from American Pharmaceutical Partners, Inc. (Schaumburg, IL), formulated at 50 mg/ml with polysorbate 80

(100 mg/ml) and benzyl alcohol (20.2 mg/ml) in water for injection with a pH of 4. PM101 was manufactured by HollisterSteir Laboratories (Spokane, WA). This stable formulation contained amiodarone (50 mg/ml) and SBE7betaCD (225 mg/ml) in a 25 mM citrate buffer at a pH of 3.7.

The amiodarone dose chosen for this study was based on the recommended U.S. human loading dose of 150 mg (Abraxis Pharmaceutical Products, 2008), which is 2.14 mg/kg in a 70-kg patient. Amiodarone IV was administered either as an infusion over 10 min or as a bolus push. In the 10 min infusion group, Amiodarone IV was diluted to 1.5 mg/ml in dextrose 5% in water and infused at a rate to deliver 2.14 mg/kg over 10 min (consistent with the approved human labeling). The Amiodarone IV bolus push group was given as an undiluted bolus push of the stock solution (50 mg/ml). PM101 (2.14 mg/kg) was administered as a bolus push of the stock solution (50 mg/ml). The vehicles of Amiodarone IV and PM101 were tested at the same dilution and infusion rates used for each formulation. A bolus push of 5% dextrose in water served as the Control group.

2.5. Study design

A total of seven dosing regimens were tested in parallel groups of 7 dogs each. These regimens consisted of 1) Control (administered as a bolus push, 2) PM101 (2.14 mg/kg administered as a bolus push), 3) Amiodarone IV (2.14 mg/kg administered as an infusion over 10 min), 4) Amiodarone IV (2.14 mg/kg administered as a bolus push), 5) PM101 Vehicle (administered as a bolus push), 6) Amiodarone IV Vehicle (administered as an infusion over 10 min), and 7) Amiodarone IV Vehicle (administered as a bolus push). Hemodynamic parameters were evaluated before dosing and at 1, 10, 15, 30, 45, and 60 min after dose initiation. The following parameters were measured: systolic aortic pressure (mm Hg), diastolic aortic pressure (mm Hg), left ventricular systolic pressure (mm Hg), and left ventricular end diastolic pressure (mm Hg). Mean aortic pressure (mm Hg) was calculated according to the formula mean aortic pressure = diastolic aortic pressure + (systolic aortic pressure − diastolic aortic pressure) / 3. The maximum and minimum rates of change of left ventricular pressure (dP/dt_{max}, dP/dt_{min}, mm Hg/s) were calculated from the left ventricular pressure measurements. Cardiac output (l/min) was calculated by the thermodilution method. Systemic vascular resistance (mm Hg/(l/min)) was calculated from the cardiac output and the mean aortic blood pressure measurements. The following electrocardiographic parameters were evaluated at the same time points: PR interval (ms), QRS interval (ms), QT interval (corrected for heart rate, QTc, ms; Fridericia, 1920), and heart rate (HR, beats/min). Average values taken from 5–15 cardiac cycles at each time point uninterrupted by interference of ectopic beats, which was less than ~3%, were used for analysis of hemodynamic parameters and electrocardiogram measurements.

2.6. Statistical analysis

The effect of treatment on hemodynamic and electrocardiographic variables was examined for statistical significance by one-way analysis of variance (ANOVA) for each time point. The Dunnett test was performed for the multiple comparisons of each treatment group with the Control group at each time point. A P value < 0.05 was considered statistically significant. All values are presented as mean ± S.E.M.

3. Results

A total of 49 dogs with an average weight of 8.6 ± 0.2 kg were used in this study. No intra-procedure mortality was observed in response to any treatment.

The hemodynamic parameters observed in dogs treated with Control, Amiodarone IV, and PM101 are presented in Figs. 1 and 2. No

significant changes were observed in any hemodynamic parameter in the Control group. Similar to Control, bolus push administration of PM101 did not exert any significant effect on hemodynamic variables compared to the Control group at any time point. In contrast, Amiodarone IV (2.14 mg/kg), administered either as an infusion over 10 min or administered as a bolus push, produced rapid and significant decreases in mean aortic pressure within 10 min after administration. This response was primarily due to a profound negative inotropic response that significantly decreased cardiac output (Fig. 2) along with a nonsignificant trend to decrease systemic vascular resistance (from 51.9 ± 3.2 at baseline to 37.1 ± 3.5 mm Hg/l/min in the 10 min infusion group and from 61.5 ± 7.9 at baseline to 44.2 ± 6.6 mm Hg/l/min in the bolus push group after 10 min). A significant compensatory increase in heart rate was seen in both Amiodarone IV groups, indicating a baroreceptor-mediated reflex response. At 60 min after dosing, the decrease in mean aortic pressure, cardiac output, and dP/dt had not returned to pretreatment levels in either of the Amiodarone IV groups.

The hemodynamic response observed in dogs treated with the vehicle of PM101 (i.e. SBE7betaCD) or with the vehicle of Amiodarone IV (i.e. polysorbate 80/benzyl alcohol) are provided in Figs. 3 and 4. The hemodynamic parameters in the group treated with bolus push of PM101 Vehicle were not different from the Control group at any time. In contrast, rapid and significant hemodynamic changes occurred in the groups treated with the Amiodarone IV vehicle delivered either as a 10 min infusion or as a bolus push. These responses observed for the
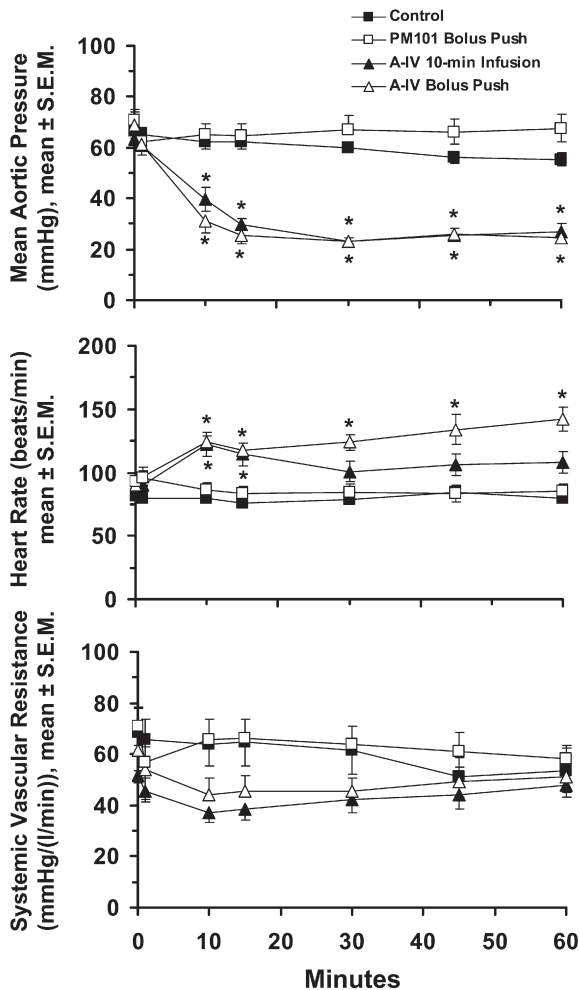

Fig. 1. The effect of Amiodarone IV (A-IV) and PM101 on mean aortic pressure, heart rate, and systemic vascular resistance in anesthetized dogs. Data presented as ± S.E.M. *P<0.05 compared with Control (ANOVA, Dunnett's test).

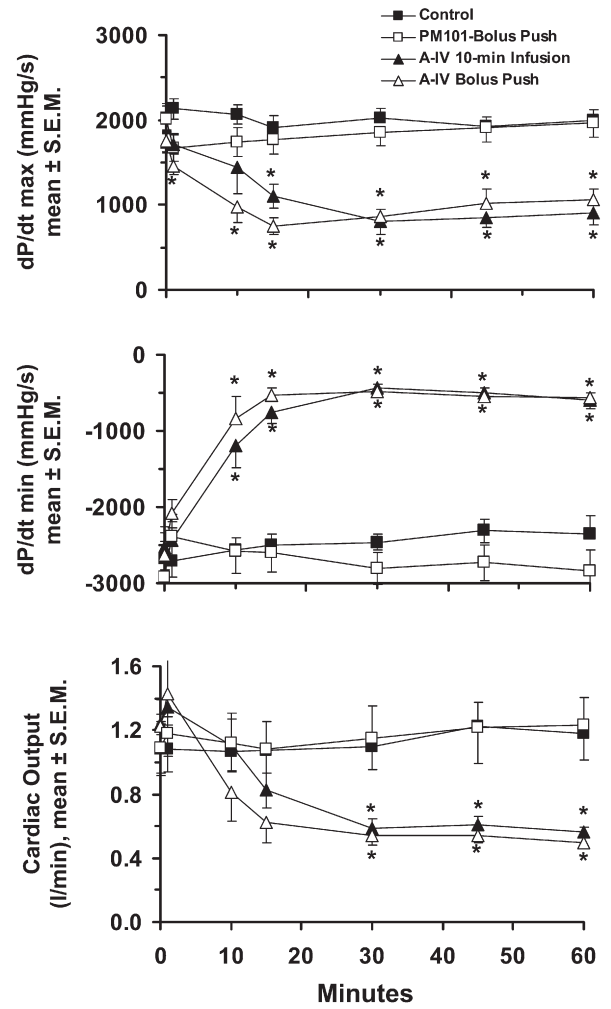Fig. 2. The effect of Amiodarone IV (A-IV) and PM101 on dP/dt and cardiac output in anesthetized dogs. Data presented as ± S.E.M. *P<0.05 compared with Control (ANOVA, Dunnett's test).

Amiodarone IV Vehicle were qualitatively and quantitatively similar to those seen for Amiodarone IV. There were no significant differences detected between the relevant Amiodarone IV and Amiodarone IV Vehicle treatments at any timepoint (P>0.05; Scheffe Test) suggesting that the hypotensive effect of the Amiodarone IV formulation was due to the cosolvents.

A summary of the electrocardiographic results is presented in Fig. 5. No significant changes in PR interval, QRS interval, or QTc occurred following administration of PM101 as a bolus, or following Amiodarone IV either as a bolus push or a 10-min infusion.

4. Discussion

In this study, the human-equivalent loading dose of commercial Amiodarone IV resulted in substantial hypotension in anesthetized dogs when administered as either a diluted 10-min infusion or as an undiluted bolus push. The hypotension appeared to be due in largest part to a profound negative inotropic effect, resulting in reduced cardiac output. The hemodynamic responses that occurred with the Amiodarone IV vehicle (i.e. polysorbate 80/benzyl alcohol) were identical to those observed for Amiodarone IV. Thus, these data, along with other previously published data, suggest that the hypotensive effects of Amiodarone IV result from the cosolvents used in its formulation (i.e. polysorbate 80/benzyl alcohol). In contrast, the comparable dose of amiodarone administered as PM101, which did
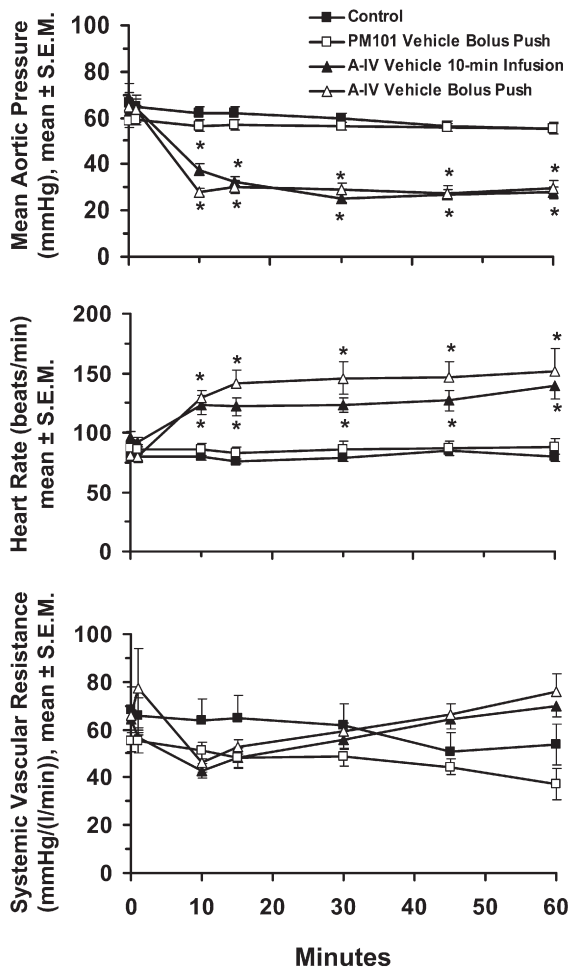
Fig. 3. The effect of Amiodarone IV (A-IV) Vehicle or PM101 Vehicle on mean aortic pressure, heart rate, and systemic vascular resistance in anesthetized dogs. Data presented as ± S.E.M. *$P < 0.05$ compared with Control (ANOVA, Dunnett's test).

head comparisons of the commercial formulation with custom-prepared aqueous formulations have also strongly implicated the cosolvents in the hypotensive response (Gough et al., 1982; Path et al., 1991; Somberg et al., 2004a). Thus, our study confirms and extends the previous reports establishing the cosolvents, polysorbate 80 and benzyl alcohol, as the responsible agents for the hypotensive effects seen with commercial preparations of Amiodarone IV.

The mechanisms responsible for the hemodynamic responses to polysorbate 80 in dogs are unclear, although an allergic-type reaction has been implicated. Increased plasma histamine correlated with the hypotensive response to polysorbate 80 in conscious dogs (Masini et al., 1985) and pretreatment with H_1 and H_2 receptor antagonists attenuated the hypotensive response. Hypotension due to polysorbate 80 in dogs occurred after an initial intravenous dose but not subsequent doses, leading to the speculation that the tachyphylaxis was due to histamine depletion of mast cells (Platou and Refsum, 1986).

In the present study, PM101 did not affect heart rate while a significant tachycardia was observed after dosing with Amiodarone IV. The tachycardia following Amiodarone IV dosing appeared to be a reflex response to the significant decrease in blood pressure. Somberg et al. (2004a) previously reported a similar reflex tachycardia with Amiodarone IV in conscious dogs; however, they also reported a slight bradycardia with an aqueous formulation of amiodarone. The lack of bradycardia with PM101 in the current study may be related to the use of an anesthetized animal model rather than a conscious animal model. The combination of α-chloralose and morphine is the standard

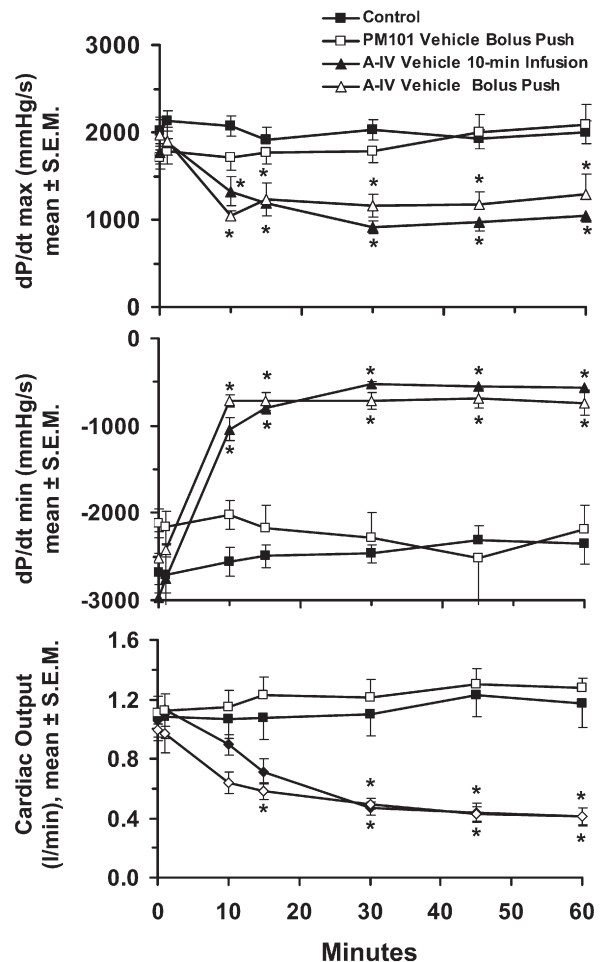not incorporate polysorbate 80 and benzyl alcohol, had no hemodynamic effects when administered as a bolus push.

That the different hemodynamic responses to intravenous amiodarone formulations observed in the present study are due to the differences in the solubilization of amiodarone is further supported by a summary of other reported hemodynamic responses to amiodarone and its various vehicles. Without exception, the previous studies that evaluated the commercial formulation of Amiodarone IV reported a large decrease in arterial blood pressure (Gough et al., 1982; Platou and Refsum, 1986; Path et al., 1991; Somberg et al., 2004a). Similarly, polysorbate 80 alone (at doses between 2 and 20 mg/kg) or in combination with benzyl alcohol produced profound reductions in arterial blood pressure in dogs and other animal models (Krantz et al., 1948; Platou and Refsum, 1986; Torres-Arraut et al., 1984; Varma et al., 1985; Masini et al., 1985; Newton and Erk, 1981; Sugiyama et al., 2001; Lessa and Tibirica 2004; Salgado et al. 2007). Thus, these previous preclinical studies established that intravenous infusions of polysorbate 80 cause hypotension and negative inotropic responses similar to those seen during treatment with the commercial formulation of Amiodarone IV that contains polysorbate 80. Benzyl alcohol may also contribute via a negative inotropic response (Yasaka et al., 1979). In contrast, when amiodarone was prepared by dissolution in ethanol and water or in other aqueous media, only minimal effects on blood pressure occurred at very high doses (e.g. 25 mg/kg) (Talajic et al., 1987; Charlier et al., 1968; Petta and Zaccheo, 1971; Gough et al., 1982; Connolly et al., 1984; Talajic et al., 1987; Bicer et al., 2000; Somberg et al., 2004a; Sugiyama et al., 2001). Head-to-

Fig. 4. The effect of Amiodarone IV Vehicle or PM101 Vehicle on left ventricular dP/dt and cardiac output. Data presented as ± S.E.M. *$P < 0.05$ compared with Control (ANOVA, Dunnett's test).
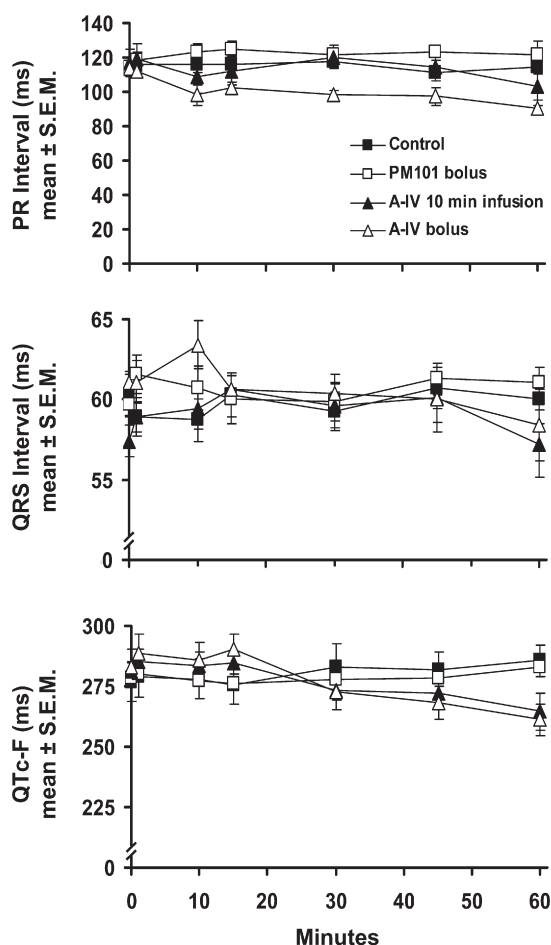
Fig. 5. The effect of Amiodarone IV (A-IV) or PM101 on surface electrocardiographic measurements. No significant differences compared with Control were found.

favors the release of drug molecules into the blood without affecting the pharmacokinetics of the drug. This concept has been demonstrated with SBE7betaCD and the intravenous sedative/hypnotic drug propofol (Egan et al., 2003). The pharmacokinetic parameters measured with the SBE7betaCD formulation of propofol and the approved lipid emulsion formulation (Diprivan®, AstraZeneca Pharmaceuticals, Wilmington, DE) were identical. Others, however, have reported that SBE7betaCD may affect the pharmacokinetics of an agent (Charman et al. 2006). That SBE7betaCD does not alter the delivery of amiodarone in PM101 compared to that of Amiodarone IV was confirmed by a relative bioavailability study in humans (Cushing et al. 2008). In that study the plasma concentration profile of PM101 was superimposable to that of Amiodarone IV. The geometric mean ratio for AUC was 1.03 and for C_{max} was 1.00 (Cushing et al. 2008).

This current study clearly demonstrates that commercial Amiodarone IV is negatively inotropic and hypotensive in dogs when administered according to the recommended diluted clinical loading dose or when administered as an undiluted bolus push. The hypotensive effect of Amiodarone IV unequivocally resulted from the cosolvents used in the commercial formulation because the vehicle alone produced similar hemodynamic effects. The novel formulation of amiodarone with SBE7betaCD (i.e. PM101), devoid of polysorbate 80 and benzyl alcohol, did not exert adverse hemodynamic effects when administered as an undiluted bolus push. This study provides a useful model for the continued search for a safe and effective Amiodarone IV formulation devoid of the hypotensive risk associated with the current commercial formulation. The extent to which these observations, and overall safety and effectiveness, may be translated to humans will require clinical studies.

5. Conflict of interest statement

Drs. Cushing and Cooper are employees of Prism Pharmaceuticals Inc., the owner of PM101. Drs. Kowey, Massey and Lipicky are paid medical and scientific consultants to Prism Pharmaceuticals Inc. Dr. Gralinski is the owner of CorDynamics Inc., the contract research organization where the studies were conducted.

Acknowledgements

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anesthetic regimen used in our laboratory because α-chloralose is believed to preserve myocardial function and produce an immobilized dog with intact cardiac reflexes (Lang et al., 1992; Holzgrefe et al., 1987). Since α-chloralose is reported to have little if any analgesic properties (Holzgrefe et al., 1987) morphine is added. Morphine may lower heart rate via central vagal stimulation and has been reported to have a direct depressant action on the sinoatrial node (Holzgrefe et al., 1987). The range of baseline heart rates across the treatment groups ranged from 81–107 beats/min in this study and is consistent with previously published data comparing α-chloralose anesthetic regimens to conscious dogs (Lang et al., 1992) and inhalation anesthetics (Wilton et al., 1988). Alternatively, the absence of an observable bradycardia with PM101 might be related to the slightly lower amiodarone dose administered, 2.14 mg/kg versus 2.5 mg/kg and 5 mg/kg.

Cyclodextrins have been commonly used as pharmaceutical excipients to aid in the preparation of aqueous formulation of drugs with poor water solubility (Loftsson et al., 2005). More than 30 pharmaceutical products containing cyclodextrins are marketed worldwide (Loftsson et al., 2005), including products intended for intravenous administration. Approved intravenous products that use SBE7betaCD, the same cyclodextrin in PM101, include voriconazole, ziprasidone, and aripiprazole.

Cyclodextrin molecules have a lipophilic central cavity and a hydrophilic surface. When in an aqueous solution, cyclodextrins form a noncovalent complex with active molecules, and the drug molecules in complex with the cyclodextrin are in rapid equilibrium with free molecules in solution. After intravenous administration, the equilibrium

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