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The hypotensive effect of intravenous amiodarone is sustained throughout the maintenance infusion period

Daniel J Cushing,* Warren D Cooper,* Michael R Gralinski† and Raymond J Lipicky‡

**Prism Pharmaceuticals, Inc., King of Prussia, Pennsylvania, †CorDynamics, Chicago, Illinois and ‡Gaithersburg, Maryland, USA*

SUMMARY

1. Hypotension frequently occurs with use of intravenous amiodarone and is managed by slowing the rate of administration. This response has been attributed to the cosolvents in the formulation and is believed to be solely related to the initial loading dose. The present study was performed to determine whether intravenous amiodarone-induced hypotension persists beyond the loading dose and into the maintenance infusion period and also whether hypotension occurs with maintenance level dosing alone.

2. Anaesthetized beagle dogs (n = 7/group) were instrumented to assess haemodynamics. Animals were treated with the human-equivalent dosing regimen (loading dose followed by maintenance infusion) of intravenous amiodarone or control (5% dextrose in water).

3. No haemodynamic changes were observed in the control group during the 6 h study. In contrast, administration of the standard intravenous amiodarone regimen produced rapid and significant decreases in mean aortic pressure, cardiac output and maximum rate of change of left ventricular pressure that persisted throughout the 6 h maintenance infusion period. Administration of amiodarone as the maintenance infusion dose alone produced haemodynamic changes that were similar in magnitude to those observed with administration of the full dosing regimen, but were delayed in onset by approximately 60 min.

4. Dosing with a cosolvent-free formulation of amiodarone (PM101) caused no haemodynamic effects during the 6 h dosing period, indicating that the cardiodepressant effects of intravenous amiodarone were due to its cosolvents.

5. These data suggest that consideration should be given to intravenous amiodarone as a potential cause for sustained hypotension during prolonged infusion.

Key words: dog, haemodynamics, intravenous amiodarone, PM101.

Correspondence: Dr Daniel J Cushing, Prism Pharmaceuticals, Inc., 1016 West Ninth Avenue, Suite 130, King of Prussia, Pennsylvania 19406, USA. Email: dcushing@prismpharma.com

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INTRODUCTION

Intravenous amiodarone is commonly and successfully used to treat cardiac arrhythmias.[1–6] Hypotension is the most common treatment-related adverse event and is thought to be related to the cosolvents (i.e. polysorbate 80 and benzyl alcohol) used to formulate intravenous amiodarone.[7–9] To minimize hypotension of intravenous amiodarone, physicians are instructed to dilute the 150 mg loading dose and infuse it over 10 min.[10] Moreover, the labelling recommends that the hypotension that develops during this infusion be treated initially by further slowing the rate of administration.[10]

Previous animal and human studies have fully characterized the haemodynamic effects associated with the loading dose of intravenous amiodarone.[7,9,11–16] We recently reported that administration of the loading dose of intravenous amiodarone produced a profound and sustained cardiac depressant effect.[16] Although administration of intravenous amiodarone was complete within 10 min, blood pressure, cardiac output (CO) and cardiac contractility remained significantly depressed for at least 1 h. This effect appeared to be due to the cosolvents (polysorbate 80 and benzyl alcohol) because administration of the cosolvents alone produces the same response. Moreover, a formulation of intravenous amiodarone devoid of the cosolvents (PM101) did not alter blood pressure, CO or cardiac contractility.[16]

The objective of the present study was to determine whether the maintenance dose of the conventional formulation of intravenous amiodarone was associated with sustained hypotension throughout the dosing period. The present study also evaluated whether such a hypotensive effect was the result of amiodarone itself or the cosolvents used in its formulation.

METHODS

Ethics

All experiments were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (National Institutes of Health NIH Publication No. 85–23, Bethesda National Institutes of Health, 1985, Guides for the Care and Use of Laboratory Animals (revised 1996)). The study protocols were reviewed and approved by the Institutional Animal Care and Use Committee of CorDynamics (Chicago, IL, USA), where the studies were performed.

Animals

Female beagle dogs, aged between 7 and 11 months (6–12 kg), were obtained from Covance Research Products (Kalamazoo, MI, USA). 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 with male dogs (i.e. class III antiarrhythmic agents).[17,18]

Surgical procedures

After an overnight fast, the dogs were pretreated with morphine (1 mg/kg, s.c.) and anaesthetized with α-chloralose (120 mg/kg, i.v.). Anaesthesia was maintained by a constant infusion of α-chloralose (35–75 mg/kg per h, i.v.) through an indwelling catheter in the saphenous or cephalic vein. An additional venous catheter was used for the administration of test drugs. Each dog was intubated and ventilated with room air supplemented with oxygen to maintain blood gases within the normal range. A Swan-Ganz thermodilution catheter was advanced through a jugular vein into the right atrium and secured in the pulmonary capillary wedge position. A solid-state, high-fidelity pressure-monitoring catheter (Millar Instruments, Houston, TX, USA) was advanced through a carotid artery into the left ventricle for measuring left ventricular and aortic pressures simultaneously. Electrocardiograms (ECGs) and haemodynamic parameters were monitored continuously 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 killed by barbiturate overdose while anaesthetized.

Study drugs

A commercial formulation of intravenous amiodarone was obtained from American Pharmaceutical Products (Schaumburg, IL, USA). Intravenous amiodarone is formulated at 50 mg/mL in a vehicle of polysorbate 80 (100 mg/mL) and benzyl alcohol (20.2 mg/mL) in water for injection. PM101 was manufactured by Hollister-Steir Laboratories (Spokane, WA, USA). This formulation contained amiodarone (50 mg/mL) and sulphobutylether-7-β-cyclodextrin (SBE7betaCD; Captisol®; Cydex Pharmaceuticals, Lenexa, KS, USA; 225 mg/mL) in a 25-mmol/L citrate buffer in water for injection at pH 3.7. Cyclodextrins are molecules with a lipophilic central core and a hydrophilic surface that are commonly used as pharmaceutical excipients to enhance the water solubility of poorly soluble drugs.[19] SBE7betaCD is used in several approved intravenous formulations (e.g. voriconazole, ziprasidone and aripiprazole) and has been shown to be without haemodynamic effects or cardiac electrophysiological effects in dogs following bolus intravenous administration.[16,20]

Study design

Four treatment groups of seven dogs each were studied: (i) control (5% dextrose in water); (ii) intravenous amiodarone loading dose followed by maintenance dose; (iii) intravenous amiodarone maintenance dose alone; and (iv) PM101 (loading dose followed by maintenance dose). The target doses used were selected to be equivalent to the doses stipulated in the US labelling for humans. The doses consisted of a loading dose of 2.14 mg/kg (150 mg/70 kg human) and/or maintenance infusion of 0.014 mg/kg per min (1 mg/min for a 70 kg human) infused over 6 h. The intravenous amiodarone loading dose was diluted to 1.5 mg/mL and administered over 10 min as described in the approved product labelling for human administration.[10] The loading dose of PM101 and control solution were administered without dilution as a bolus. The control group received an equivolume infusion of 5% dextrose in water to match the PM101 group. The study duration of 6 h was chosen based on the experience of this laboratory in maintaining haemodynamic stability in anaesthetized dogs over this time period.

Haemodynamic parameters were evaluated prior to dosing and at 1, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after beginning dosing. The following parameters were measured or calculated: mean aortic pressure (MAP), cardiac output (CO), maximum rate of change of left ventricular pressure (dP/dt_{max}) and systemic vascular resistance (SVR). The following electrocardiographic parameters were evaluated at the same time points: PR interval, QRS interval, QT interval (corrected for heart rate (HR); QTc) and HR. Average values taken from five to 15 cardiac cycles at each time point were used for analysis of haemodynamic parameters and ECG measurements.

Statistical analysis

The effect of treatment on haemodynamic variables was examined for statistical significance by one-way analysis of variance (ANOVA) for each time point. Dunnett's test was performed for multiple comparisons of each treatment group with the control group at each time point. A $P < 0.05$ was considered significant. All values are presented as the mean ± SEM. Based on the results from a previous study in dogs,[16] a sample size of seven animals per group will provide at least 80% power to detect a difference between each treatment group and the control group.

RESULTS

Administration of intravenous amiodarone resulted in a rapid and significant decrease in MAP of approximately 60% compared with control (Fig. 1a). The onset occurred within 10 min and the effect persisted throughout the 6 h of the experiment. Cardiac output was significantly decreased by intravenous amiodarone by approximately 60% compared with control (Fig. 2a). Similar to the change in MAP,

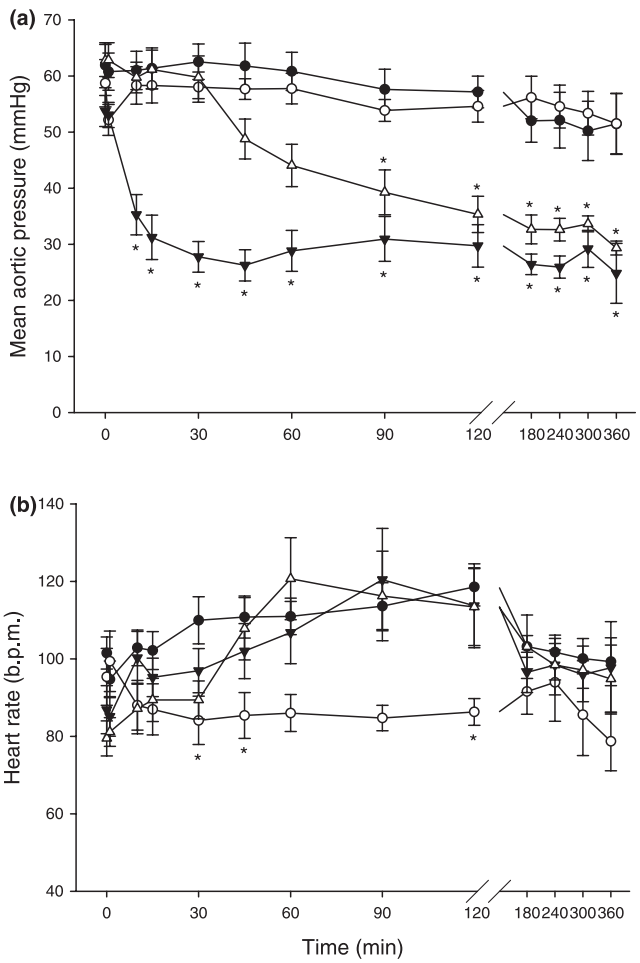

Fig. 1 Effects of intravenous amiodarone and PM101 on (a) mean aortic pressure (MAP) and (b) heart rate in anaesthetized dogs. ●, control; ○, PM101 loading dose and maintenance infusion; ▼, intravenous amiodarone loading dose and maintenance infusion; △, intravenous amiodarone maintenance infusion alone. Data are the mean ± SEM ($n = 7$/group). *$P < 0.05$ compared with control (ANOVA, Dunnett's test). The doses for each formulation were a loading dose of 2.14 mg/kg followed by a maintenance infusion of 0.14 mg/kg per min. The loading dose of PM101 was delivered as a bolus and the loading dose of intravenous amiodarone was infused over 10 min.

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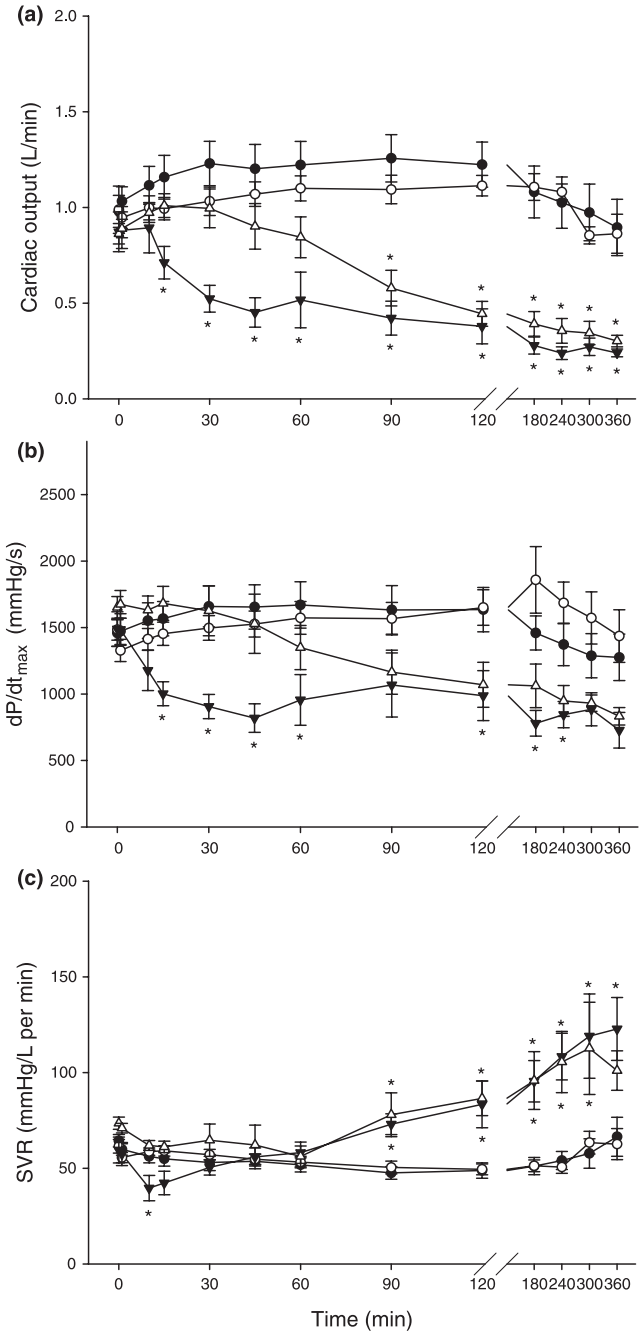

Fig. 2 Effects of intravenous amiodarone and PM101 on (a) cardiac output (CO), (b) maximum rate of change of left ventricular pressure (dP/dt_{max}) and (c) systemic vascular resistance (SVR) in anaesthetized dogs. ●, control; ○, PM101 loading dose and maintenance infusion; ▼, intravenous amiodarone loading dose and maintenance infusion; △, intravenous amiodarone maintenance infusion alone. Data are the mean ± SEM (n = 7/group). *$P < 0.05$ compared with control (ANOVA, Dunnett's test). The doses for each formulation were a loading dose of 2.14 mg/kg followed by a maintenance infusion of 0.14 mg/kg per min. The loading dose of PM101 was delivered as a bolus and the loading dose of intravenous amiodarone was infused over 10 min.

the onset of the decrease in CO occurred within 15 min and persisted throughout the experiment. Compared with control, there was an initial transient, but significant, decrease in SVR in the intravenous amiodarone group (Fig. 2c). By 90 min, SVR was significantly increased in the intravenous amiodarone group. There was a significant negative inotropic effect, as evidenced by the rapid, significant and prolonged decrease in dP/dt_{max} (Fig. 2b). The time-course of this change was similar to that observed for MAP and CO. Heart rate in the control group fluctuated over the course of the experiment (Fig. 1b), precluding a meaningful comparison of changes in any treatment group relative to control.

We also examined the effect of the maintenance infusion of intravenous amiodarone alone (without administration of the loading dose) on haemodynamics. Similar to that observed with the standard dosing regimen, administration of the maintenance dose only produced hypotension. There were significant decreases in MAP, CO and dP/dt_{max} and a significant increase in SVR (Figs 1,2). These effects were of similar magnitude as those observed with administration of the loading dose followed by maintenance dosing, but demonstrated a delayed onset. The onset of the observed decreases in MAP, CO and dP/dt_{max} occurred approximately 1 h after dose initiation. Likewise, the increases in SVR and dP/dt_{min} occurred 1 h after dose initiation.

Administration of a cosolvent-free formulation of amiodarone (PM101) was devoid of significant effect on MAP, CO, dP/dt or SVR compared with control (Figs 1,2). Figure 1b illustrates that, in general, HR in the PM101-treated group remained relatively unchanged from baseline; however, because HR in the control group increased, a significant difference was noted between 0.5 and 2 h.

No changes in PR, QRS, or QTc intervals were found in any treatment group at any time point (data not shown).

DISCUSSION

The results presented in here are the first to demonstrate that the hypotensive response to amiodarone i.v. occurs not only during and shortly after administration of the loading dose, but is sustained during continuous infusion of a maintenance dose. Indeed, amiodarone i.v. administered as the maintenance dose alone resulted in a similar reduction in MAP as was seen when the loading dose preceded the maintenance infusion. Presumably, this response is due to the cosolvents (i.e. polysorbate 80 and benzyl alcohol) used to formulate intravenous amiodarone.[7,15] In contrast with the conventional formulation of intravenous amiodarone, a formulation of amiodarone devoid of the cosolvents (i.e. PM101) did not induce hypotension with either rapid loading or maintenance dosing.

The onset of the hypotensive effect of the conventional formulation of intravenous amiodarone occurred within 10 min and was sustained over 6 h. The initial period of hypotension was due to decreases in both CO and SVR. However, the decrease in SVR was transient and reversed to become a significant increase after approximately 60 min. Therefore, the hypotension observed after 60 min was the result of a sustained decrease in CO. The observed decrease in CO was most likely due to a rapid and sustained decrease in contractility, as indicated by dP/dt_{max}. The temporal relationship between the decrease in contractility and CO was similar, as was the magnitude of the decrease. Fluctuations in HR in the control group over the course of the experiment precluded a meaningful comparison of changes in any treatment group relative to control. Although changes in HR were observed in the intravenous amiodarone groups, HR did not appear to contribute to the hypotension observed. Therefore, it may be concluded that the direct inotropic effect was the primary reason for the hypotension: because HR was relatively unchanged, the decrease in CO was due to decreased left ventricular stroke volume.

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We and others have reported previously an increase in HR with administration of the loading dose of the conventional formulation of intravenous amiodarone, which was attributed to a baroreceptor reflex.[15,16] Administration of the loading dose of intravenous amiodarone formulations devoid of polysorbate 80 and benzyl alcohol do not cause hypotension or increases in HR.[15,16] One potential difference between the reflex tachycardia reported by these laboratories and those of others is the dose of amiodarone. The studies reported here used doses of approximately 2 mg/kg, whereas those reporting blockade of sympathetic activity and bradycardia were using doses of 5 mg/kg or greater.

The first description of the haemodynamic response to intravenous amiodarone and the cosolvent polysorbate 80 in dogs was by Gough *et al.*[7] These investigators reported an immediate arterial hypotension of intravenous amiodarone formulated with polysorbate 80, but not amiodarone formulated with ethanol. These authors further reported that polysorbate 80 alone produced a similar response to that of amiodarone formulated with polysorbate 80. We reproduced these findings separately as part of characterizing the validity of the dog model to evaluate the haemodynamic effects of PM101.[16] To address the potential species differences in the haemodynamic response to intravenous amiodarone formulations, we are currently evaluating both the conventional formulation of intravenous amiodarone (with polysorbate 80) and PM101 (devoid of polysorbate 80) in a primate model. Preliminary data suggest that the primate is less sensitive to polysorbate 80 than the dog. Together with the report from Lessa and Tibirica[21] in the rabbit, it may be that there is significant species variability in the haemodynamic response to intravenous amiodarone and its excipients.

A limitation of the present study is the absence of a cyclodextrin-alone comparison group. Although we have reported on the lack of any acute (up to 1 h) haemodynamic effect of the cyclodextrin,[16] the absence of such a group in the present study as a comparator precludes clear differentiation of cardiac depressant effects of intravenous amiodarone with a potential pressor effect of the cyclodextrin over the 6 h experimental period.

The results from the present study confirm the previously reported hypotensive liability of the conventional formulation of intravenous amiodarone[7,9,11–16] and extend the observation of hypotension to the maintenance infusion period. Moreover, these data indicate that administration of the maintenance dose alone, without having administered the loading dose, can produce significant hypotension. These data suggest that consideration should be given to intravenous amiodarone as a potential cause for sustained hypotension during prolonged infusion. The absence of a hypotensive effect of PM101 supports the notion that hypotension results in largest part from the cosolvents used in intravenous amiodarone.

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