Dronedarone Effects on Atrial and Ventricular Electrophysiology in Conscious Dogs

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Atrial and ventricular electrophysiological assessments in conscious dogs are relevant models to interrogate the selectivity of potential antiarrhythmic drugs. We investigated the selective effects of dronedarone (DRO) on atrial and ventricular effective refractoriness using a conscious dog model. Male beagle dogs (n=5, 8-11 kg) were surgically instrumented with telemetry devices and two sets of bipolar electrodes placed on the right atrium and the right ventricular outflow tract to determine the atrial and ventricular effective refractory periods (AERP and VERP). One week after surgery, dogs received vehicle (β-cyclodextrin/mannitol 0.033 mL/kg/min) and DRO (0.033, 0.067 and 0.167 mg/kg/min) every 30 minutes. Dose dependent prolongation of AERP, but not VERP, was observed with DRO administration. At 300 msec cycle length, AERP was significantly increased by 19%, 31% and 46% with 1, 2 and 5 mg/kg of DRO respectively, compared to vehicle. At 400 msec cycle length, a significant increase of 44% in AERP was observed only with 5mg/kg DRO as compared to vehicle. Arterial blood pressure, heart rate, P-wave duration, and QTc interval values were unchanged throughout the experiment. Both vehicle and DRO (1, 2 and 5 mg/kg) had no significant effect on any of these cardiovascular parameters except P-wave duration which was significantly increased by 5% with 5mg/kg DRO as compared to vehicle. In summary, dose-dependent prolongations of AERP, but not VERP, were observed with DRO. This model possesses utility as a paradigm to determine the differential efficacy of test articles on atrial and ventricular refractoriness.

Support: CorDynamics, Inc.

Introduction

Atrial fibrillation is one of the most common and debilitating type of sustained cardiac arrhythmia, with rising incidence in the past decades. It is projected that 5.6 million Americans will have the disease by 2050. Atrial fibrillation is associated with increased morbidity and mortality and is therapeutically challenging. New antiarrhythmic drugs with higher efficacy and good safety profiles are urgently needed.

Drug discovery efforts have focused on identifying safer and more effective atrial-selective agents for treating AF; however robust and relevant nonclinical models of atrial and ventricular electrophysiology are needed to examine these new molecular entities. Animal models of atrial fibrillation usually focus on acute anesthetized paradigms or complex electrophysiological assessments not particularly suited for efficacy examinations with multiples compounds.

The present study was designed to assess the conscious dog as a model to interrogate the selectivity of new compounds on atrial and ventricular effective refractoriness.

Summary

- Dose dependent prolongation of AERP, but not VERP, was observed with dronedarone administration. At 300 msec cycle length, AERP was significantly increased by 19%, 31% and 46% with 1, 2 and 5 mg/kg of dronedarone respectively, compared to vehicle. At 400 msec cycle length, a significant increase of 44% in AERP was observed only with 5mg/kg dronedarone as compared to vehicle.
- A significantly increase of 5% in P-wave duration was observed with 5mg/kg dronedarone, as compared to vehicle.
- Both vehicle and dronedarone (1, 2 and 5 mg/kg) had no significant effect on arterial blood pressure, heart rate, PR interval, QRS interval, and QTcVDW interval.
- Analysis of blood samples from dogs showed plasma concentration levels at the highest dronedarone dose (5mg/kg) of 1216 ng/mL, 10 times higher than the steady state plasma levels for dronedarone used clinically (≈120ng/mL).

Objectives

Investigate the selectivity of dronedarone on atrial and ventricular effective refractoriness using a conscious dog model.

Methods

Surgical Preparation: Male beagle dogs (n=5, 8-11 kg) were surgically instrumented with telemetry devices to monitor blood pressure, heart rate and electrocardiogram. A blood pressure catheter was positioned in the femoral artery and advanced cranially into the abdominal aorta, the presence of acceptable arterial pressure waveforms was verified by computer, and the catheter was secured to the femoral artery with suture. A right thoracotomy was performed for the placement of the ECG recording leads directly onto the heart. The positive ECG lead was secured to the ventricular epicardium near the ventricular apex, while the negative lead was secured to the right atrium. Additionally, two bipolar electrodes were placed on the right atrium for the eventual stimulation and measurement of atrial effective refractory period (AERP). One bipolar plunge electrode was sutured near the right ventricular outflow tract for eventual stimulation to determine the ventricular effective refractory period (VERP). The wires from each bipolar electrode were exteriorized and proper signal transmission was confirmed for both the ECG electrodes and ERP electrodes prior to closure of the implantation sites.

Experimental Plan: Approximately one week after surgery, continuous telemetry monitoring (DSI, St. Paul, MN) was initiated. Electrophysiology testing was accomplished by placing the dog in a restraint sling and connection of the pacing wires onto an external electronic stimulator (Grass Technologies, West Warwick, RI) for programmed electrical stimulation (AERP, VERP). On the day of electrophysiology experimentation, the conscious dog was placed in a sling restraint for the entire treatment period. Dronedarone was infused in escalating doses (0.033, 0.067 and 0.167 mg/kg/min) every 30 minutes. The electrophysiology measurements were conducted during the latter 20 minutes of the vehicle (β-cyclodextrin/mannitol 0.033 mL/kg/min) and dronedarone administrations. Atrial and ventricular refractory period measurements were performed via the previously implanted electrodes.

AERP measurements: For determination of AERP, hearts experienced cycles of 8 paced beats of atrial origin (S_1) at twice electrical diastolic threshold, using two discrete cycle lengths (400 msec, 300 msec). The eight paced beat was followed by an extra atrial stimulus (S_2) delivered at varying coupling intervals from the eight beat train of S_1. The coupling time that failed to elicit an S_2 stimulus was noted as the AERP.

VERP measurements: For determination of VERP, hearts were paced at the ventricle at twice electrical diastolic threshold, using two discrete cycle lengths (400 msec, 300 msec). An extra atrial stimulus (S_2) was delivered at varying coupling intervals. The S_2 coupling time that failed to elicit a ventricular response as determined by inspection of the ECG was noted as the VERP.

Plasma concentration of Dronedarone: Blood samples were obtained in presence of K_2 EDTA at 10 and 30 minutes of each infusion period. Plasma was separated, frozen on dry ice, and stored at -80°C until determination of dronedarone concentration.

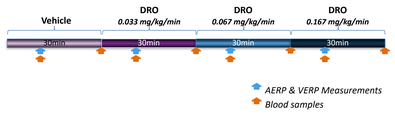

Figure 1. *Experimental design. DRO- Dronedarone*

Effects of Dronedarone on Atrial Effective Refractory Period in Conscious Telemeterized Male Beagle Dogs

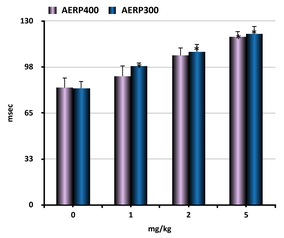

Figure 2. *Effects of dronedarone 1, 2 and 5 mg/kg (0.033, 0.067 and 0.167 mg/kg/min for 30 min IV), or vehicle (β-cyclodextrin/mannitol 0.033 mL/kg/min) on AERP in conscious dogs. Values are expressed as mean±SEM, with n=5. *p<0.05, vs. vehicle, determined by using a one-way ANOVA followed by post hoc Newman-Keuls test.*

Effects of Dronedarone on Ventricular Effective Refractory Period in Conscious Telemeterized Male Beagle Dogs

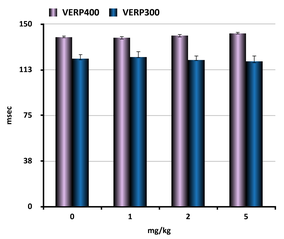

Figure 3. *Effects of dronedarone, 1, 2 and 5 mg/kg (0.033, 0.067 and 0.167 mg/kg/min for 30 min IV), or vehicle (β-cyclodextrin/mannitol 0.033 mL/kg/min) on VERP in conscious dogs. Values are expressed as mean±SEM, with n=5. *p<0.05, vs. vehicle determined by using a one-way ANOVA followed by post hoc Newman-Keuls test.*

Effects of Dronedarone on QTcVDW Interval and P-wave duration in Conscious Telemeterized Male Beagle Dogs

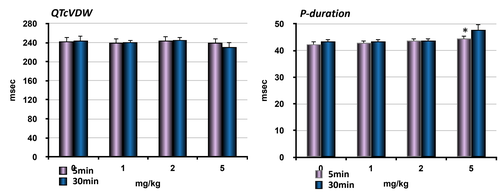

Figure 4. *Effects of dronedarone, 1, 2 and 5 mg/kg (0.033, 0.067 and 0.167 mg/kg/min for 30 min IV), or vehicle (β-cyclodextrin/mannitol 0.033 mL/kg/min) on P-wave duration and corrected QTc interval (Van de Water's formula) in conscious dogs. Values are expressed as mean±SEM, with n=5. *p<0.05, vs. vehicle determined by using a one-way ANOVA followed by post hoc Newman-Keuls test.*

Effects of Dronedarone on Arterial Blood Pressure in Conscious Telemeterized Male Beagle Dogs

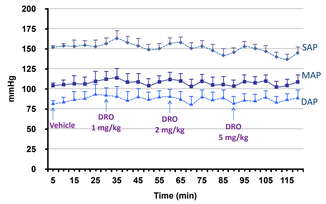

Figure 5. *Effects of dronedarone, 1, 2 and 5 mg/kg (0.033, 0.067 and 0.167 mg/kg/min for 30 min IV), or vehicle (β-cyclodextrin/mannitol 0.033 mL/kg/min) on arterial blood pressure. Values are expressed as mean±SEM, with n=5.*

Plasma Concentration of Dronedarone during Continuous Infusion of Escalating Doses every 30 minutes in Conscious Telemeterized Male Beagle Dogs

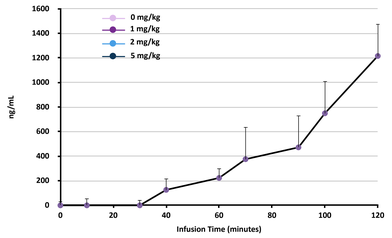

Figure 6. *Plasma levels of dronedarone during continuous intravenous infusion of escalating doses (0.033, 0.067 and 0.167 mg/kg/min) every 30 minutes in conscious telemeterized male beagle dogs. Values are expressed as mean±SEM, with n=5.*

Conclusion

Dose-dependent prolongations of AERP, but not VERP, were observed with dronedarone. Conscious dog model possesses utility as a paradigm to determine the differential efficacy of test articles on atrial and ventricular refractoriness.

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