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Dronedarone attenuates the duration of atrial fibrillation in a dog model of sustained atrial fibrillation

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Abstract: Atrial fibrillation (AF) is a supraventricular arrhythmia that leads to a decrease in cardiac output and impairs cardiac function and quality of life. Dronedarone has an atrial-selective property and has been used for management of AF in humans, but limited information is available in dogs. This study was designed to evaluate efficacy of dronedarone in attenuating the duration of AF in dog model of sustained AF. Six beagle dogs were anesthetized with isoflurane and instrumented to measure atrial action potential duration (aAPD) and atrial effective refractory period (AERP). Then AF was induced by rapid right atrial pacing (20 V, 40 Hz) simultaneously with infusion of phenylephrine (2 μg/kg/min, intravenously) for 20 min. The duration of sustained AF was recorded, and the animals were allowed to recover. Dronedarone was given at a dose of 20 mg/kg, BID, orally for 7 days. On the last day, the dogs were anesthetized again to record aAPD and AERP, and AF was induced with the same procedure as described above. The results showed that after dronedarone administration the aAPD was lengthened significantly from 76.4 ± 4.2 ms to 91.2 ± 3.9 ms (P<0.05) and AERP was prolonged significantly from 97.5 ± 2.8 ms to 120 ± 4.8 ms (P<0.05). The duration of sustained AF was also significantly attenuated after receipt of dronedarone (P<0.05). It can be suggested that oral dronedarone attenuates the duration of sustained AF in a dog model of AF by extending the AERP more than the aAPD, causing post-repolarization refractoriness. Hence, dronedarone may be useful for management of AF in dogs.

Key words: atrial fibrillation, dog, dronedarone, post-repolarization refractoriness

Introduction

Atrial fibrillation (AF) is a form of supraventricular arrhythmias. Its prevalence has been observed in large and giant breeds (i.e., Irish Wolfhound, Great Dane, Newfoundland, and Doberman pinscher) and small breeds with underlying heart diseases [14, 23, 37]. The consequences of AF are decreased cardiac output and impaired mechanical function of the heart and quality of life [32]. Rhythm control and rate control strategies have been suggested for management of AF in dogs [32]. In clinical practice, rhythm control either by electrical car-

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dioversion or by pharmacological conversion has demonstrated more risk to patients than control of the ventricular response rate due to the need for general anesthesia and pharmacological side effects [9]. Therefore, rate control strategy is preferred by several practitioners. Besides digoxin, diltiazem, quinidine, and atenolol, amiodarone has been used widely in veterinary medicine since it was demonstrated to restore sinus rhythm and reduce ventricular response rate in dogs with AF [17, 26, 28, 33]. Similar to in humans, the adverse effects of these antiarrhythmic drugs have been reported in dogs [1, 2, 16, 28, 33].

Dronedarone, a class III antiarrhythmic drug, has been approved for management of AF in humans by FDA since 2009 [24, 34]. Several clinical trials have been demonstrated the advantages of dronedarone in restoring sinus rhythm as well as controlling ventricular response rate in AF patients without heart failure [15, 20, 35, 36]. Furthermore, dronedarone prevents AF recurrences and prolongs the time to onset of first AF occurrence in patients at high risk of AF [27]. Our previous study in anesthetized dogs showed that dronedarone reduced the heart rate and lengthened the PQ interval [30]. A study in conscious dogs instrumented with telemetry units showed that dronedarone (20 mg/kg, twice a day (BID), orally) prolonged the PQ interval without effects on cardiac inotropy and lusitropy [31]. It has been reported in canine isolated coronary-perfused atria that the efficacy of acute dronedarone (10 μmol/l) in preventing AF induced by acetylcholine infusion and terminating persistent AF is poor when compared with amiodarone [6]. However, previous data in anesthetized dogs indicated that acute administration of dronedarone resulted in electrophysiological actions similar to those produced by amiodarone [21]. Since the efficacy of dronedarone is controversial, the efficacy of dronedarone in management of AF *in vivo* should be confirmed. In addition, the adverse effect of dronedarone at a therapeutic dose has not been established in dogs. This study was designed to 1) evaluate effects of oral dronedarone on prevention of atrial fibrillation and 2) investigate its mechanism of prevention related to atrial electrophysiology in a dog model of sustained atrial fibrillation. This experiment may support the use of dronedarone for management of AF in clinical AF dogs.

Materials and Methods

Approvals

This study was approved by the Institutional Animal Care and Use Committee of QTest Labs, Ltd., Columbus, OH, USA (protocol number: SPD14-022). All experimental animal procedures were performed in compliance with QTest Institutional Animal Care and Use Committee regulations, and followed the guidelines outlined in the *Guide for the Care and Use of Laboratory Animals* [25].

Animals

Six healthy mature beagles (*Canis familiaris*) of either gender were purchased from Marshall BioResources (North Rose, NY, USA). They were housed individually from the time of arrival to the end of the study in a dog run maintained at a temperature of 21 ± 2°C and a relative humidity of 50 ± 20%, with a 12 h:12 h light:dark cycle. All animals were received commercial chow twice daily, and water was provided *ad libitum* in stainless steel containers. Physical examination, routine lead II electrocardiogram (ECG) recording, complete blood count, and blood chemistry analysis were performed to evaluate healthy status in all dogs before the beginning of the experiment. Surgical procedures were started a fasting period of at least 6 h period of fasting.

Surgical procedures for measurement of atrial effective refractory period (AERP), atrial action potential duration (aAPD), and induction of sustained AF

All dogs were given butorphanol (0.1 mg/kg, intravenously) 10 min before receiving propofol (4–6 mg/kg, intravenously). Orotracheal intubation was performed and ventilated mechanically with an ascending-bellows, volume-cycled, pressure-regulated ventilator. The ventilator was set to deliver a tidal volume of 12–15 ml/kg (maximum allowed pressure, 20 cmH_2O) at a rate of 8 to 12 breaths per min, sustaining the end-tidal partial pressure of CO_2 between 35 and 45 mmHg and that of O_2 greater than 80 mmHg. The endotracheal tube was connected to a circle anesthetic rebreathing circuit, and anesthesia was maintained with isoflurane in oxygen delivered by a use of vaporizer. The end-tidal inhalant concentration was maintained between 1.4–1.6%. Body temperature was maintained at 36.5–37°C by a warm water heating pump. Each animal was shaved and scrubbed at the surgical areas and prepared by aseptic

technique (left femoral triangle and left jugular area).

A Mikro-Tip catheter pressure transducer (5Fr, Millar, Inc., Houston, TX, USA) was inserted into the left femoral artery and advanced to the aortic arch for measuring systemic arterial blood pressure. With the help of fluoroscope guidance, a monophasic action potential catheter was inserted through the left jugular vein and pushed against the endocardium of the right atrium to obtain the aAPD. AERP was obtained by using a programmable electrical stimulator. Extrastimuli were introduced at premature coupling intervals (S_1–S_2) by progressively shortening by 10 ms the pacing cycle length until atria failed to depolarize. Then, the pacing cycle length was progressively increased by 5 ms until it caused atrial depolarization. The AERP was the longest S_1-S_2 interval that failed to cause atrial depolarization.

Lead II ECG data were monitored for rhythm and rate. After obtaining the aAPD and AERP, a bipolar pacing catheter was positioned at the right atrial appendage through the left jugular vein for induction of AF. Sustained AF was induced according to the method in a previous publication [18]. Briefly, the right atrial appendage was pacing at a rate of 40 Hz with square waves of 20 V and 2 ms duration. Simultaneously, phenylephrine (PE, 2 μg/kg/min) (Baxter Healthcare Corporation, Deerfield, IL, USA) was infused constantly through a peripheral intravenous catheter placed inside the right cephalic vein until the end of the session. After 20 min of rapid atrial pacing (RAP), the pacing was stopped, and the duration of AF was observed. AF was identified by (1) the presence of an irregular rapid ventricular response, (2) absence of a P wave, (3) presence of low-frequency irregular oscillations (f waves), and (4) a presence of irregular systemic arterial pressure pulses that were variable in amplitude and had a pulse deficit. At the end of experiment, all vessels were sutured with 8–0 Prolene. Tissues and muscles were sutured with absorbable 3–0 suture materials. Skin was closed with sterile staples. Butorphanol (0.05–0.4 mg/kg, once a day, subcutaneously; Abbott Laboratories, North Chicago, IL, USA), acepromazine (0.05–0.2 mg/kg, once a day, subcutaneously; Butler Animal Health Supply, Dublin, OH, USA), and cefazolin (15 mg/kg, once a day, subcutaneously; Butler Animal Health Supply, Dublin, OH, USA) were administered for 7 days.

Experimental procedures

After instrumentation, dogs were allowed to stabilize for at least 30 min. Then ECG, blood pressure (BP), aAPD, and AERP data were obtained. After all data were collected, sustained AF was induced. The incidence and duration of AF were recorded after pacing was stopped. The dogs were allowed to recover, and dronedarone (20 mg/kg, BID, orally) was given for 7 days beginning the next day. The dose of dronedarone was chosen based on our previous experiment in conscious dogs instrumented with a telemetry unit [31]. After 7 days of drug administration, the dogs were anesthetized and instrumented as described earlier for obtaining ECG, BP, aAPD, and AERP data. Each dog was infused with PE at a dose of 2 μg/kg/min. Simultaneously, RAP was initiated as described earlier. After 20 min of pacing, pacing was stopped, and the cardiac rhythm was monitored. Then, the concentration of PE was increased to 4 μg/kg/min, and the atrium was paced again for 20 min. At the end of the experiment, all animals were allowed to recover, and postoperative care was performed for 7 days. Then all dogs were transferred back to the in-house colony.

Data analysis

ECG and BP were analyzed for heart rate (HR) or ventricular response rate (VR) and mean blood pressure (MBP) before dosing (at baseline before PE infusion with RAP and at 20 min during PE infusion with RAP) and 7 days after dosing (at baseline, at 20 min in the first trial during PE infusion [2 μg/kg/min] with RAP, and at 20 min in the second trial of PE infusion [4 μg/kg/min] with RAP] by using the ecgAuto software (EMKA Technologies, Falls Church, VA, USA). APD_{70} was defined as the action potential duration at 70% repolarization of the aAPD. The APD_{70} and AERP were obtained before dosing and 7 day after dosing. Post-repolarization refractoriness (PRR) was calculated as the percent change of differences between the AERP and atrial APD_{70}. In atria, the AERP usually coincided with APD_{70} to APD_{75} [7]. The duration of sustained AF after dosing was calculated as the averaged of the duration of AF from the first and second trials.

Statistical analysis

Statistical analyses were performed with commercially available software. Data were presented as the mean ± standard error of the mean. All data points were averaged from 60 s of recording. Differences between before dosing and after dosing were determined by paired *t*-test. The percent change from before dosing was

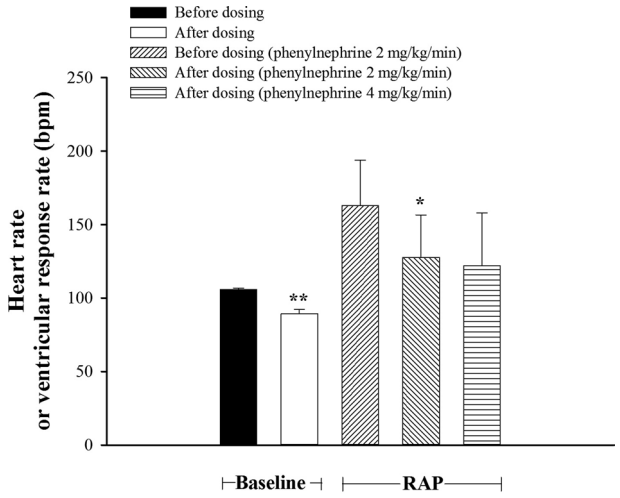

Fig. 1. Plots of heart rate (at baseline before the beginning of phenylephrine infusion) and ventricular response rate (during rapid atrial pacing, RAP) for before and after dosing with oral dronedarone administration (20 mg/kg, BID) for 7 days in dogs while they were anesthetized with isoflurane. *Significant difference when compared with the ventricular response (VR) during phenylephrine (PE) infusion simultaneous to RAP before dosing (P<0.05). **Significant difference when compared with before dosing at baseline (P<0.01).

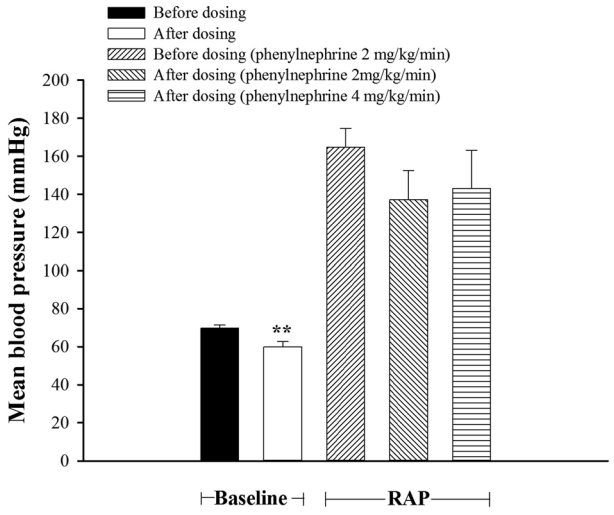

Fig. 2. Plots of mean blood pressure at baseline (before the beginning of phenylephrine infusion) and rapid atrial pacing (RAP) for before and after dosing with oral dronedarone (20 mg/kg, BID) for 7 days in dogs while they were anesthetized with isoflurane. **Significant difference when compared with before dosing at baseline (P<0.01)

calculated for the PRR parameter, and the difference was determined by Student's *t*-test. Fisher's exact tests were used to compare the incidence of reduction of AF duration between before and after dosing. A probability value of P<0.05 was considered to be significant.

Results

Before the onset of PE infusion (baseline) while the dogs were anesthetized, HR and MBP (before dosing) were 106 ± 1.0 beats per min (bpm) and 69.7 ± 1.7 mmHg, respectively (Figs. 1 and 2). After oral dronedarone administration (20 mg/kg, BID) for 7 days, HR and MBP were significantly reduced (P<0.05), by 15.6% and 14.0%, respectively, when compared with before dosing. During RAP performed simultaneous to PE infusion before dosing, VR was 163 ± 31 bpm. After dosing, VR during RAP and PE infusion at 2 μg/kg/min declined significantly (21.6%, P<0.05), while VR during RAP and PE infusion at 4 μg/kg/min did not change when compared with that before dosing (Fig. 1). MBP before dosing was 137.2 ± 15.4 mmHg. After dosing, neither MBP during RAP and PE infusion at 2 μg/kg/min nor MBP during RAP and PE infusion at 4 μg/kg/min were different from MBP during RAP and PE infusion before dosing (Fig. 2).

In response to dronedarone, the APD_{70} of the atrium showed a significant increase of 19.3% compared with that before dosing (before dosing, 76.4 ± 4.2 ms vs. after dosing; after dosing, 91.2 ± 3.9 ms; P<0.001). The AERP also showed a significant increase, increasing 23.1% compared with that before dosing (before dosing, 97.5 ± 2.8 ms; after dosing, 120.0 ± 4.8; P<0.01). Hence, PRR showed a significant increase of 36.7% compared with before dosing (from 21.1 ± 4.6 ms to 28.8 ± 6.4 ms; P<0.05).

Before dosing, atrial fibrillation persisted after PE infusion and RAP in all dogs for an average of 88.8 s (ranging from 441.7 to 1.89 s) after cessation of pacing (Fig. 3). After 7 days of dronedarone administration, sustained AF was induced in 5 dogs in which the average duration of sustained AF was reduced to 5.7 s (ranging from 4.3 to 10.7 s). While it was not possible to induce sustained AF in one dog (Fig. 4), the duration of sustained AF was increased in one dog (from 1.9 to 5.8 s). Therefore, the overall percentage of dogs in which dronedarone attenuated the duration of AF in dogs model of sustained AF was 83.3% (5/6 dogs, P<0.05).

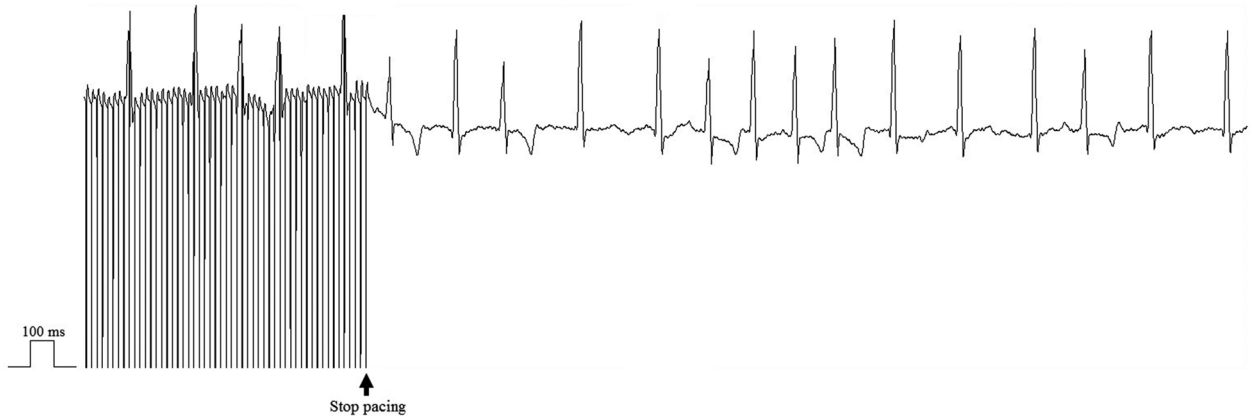

Fig. 3. Lead II electrocardiogram in an anesthetized dog with rapid atrial pacing (40 Hz, 20 V, and 2 ms) and phenylephrine infusion (2 μg/kg/min). Atrial fibrillation characterized by fibrillatory waves that varied in amplitude, shape, and timing occurred after cessation of rapid atrial pacing.

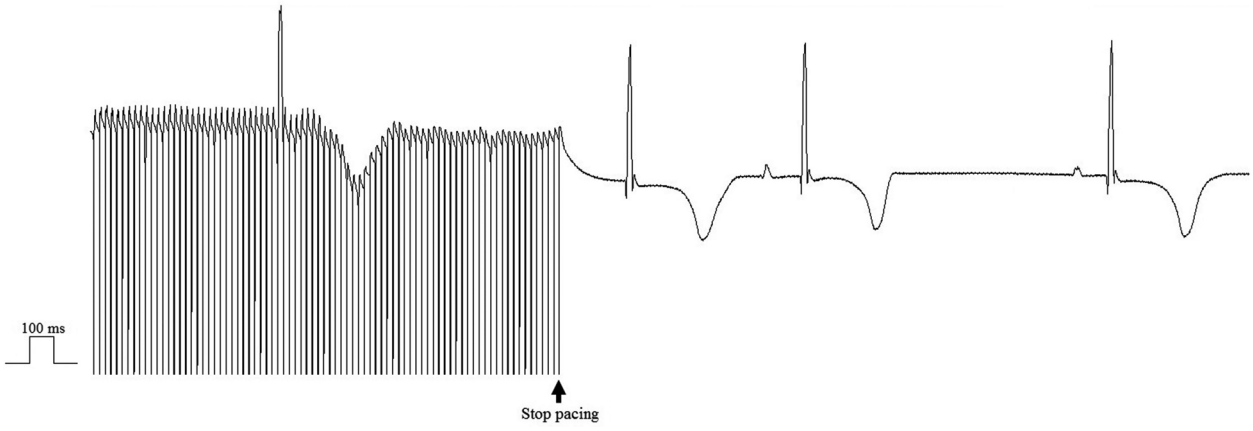

Fig. 4. Lead II electrocardiogram in an anesthetized dog treated with dronedarone (20 mg/kg, BID, orally) for 7 days. Atrial fibrillation was induced by rapid atrial pacing (40 Hz, 20 V, and 2 ms) and phenylephrine infusion (2 μg/kg/min), and it was converted to normal sinus rhythm soon after rapid atrial pacing was stopped.

Discussion

The present study demonstrated that dronedarone was effective against experimentally induced sustained AF. The sustained AF used in this study was induced by RAP with simultaneous PE infusion. According to a previous publication, PE was used to elevate systemic arterial pressure, which would increase stimulation of vagal efferents via the baroreceptor reflex [18]. Since vagal fibers in atria are heterogeneously distributed, stimulation of the vagus nerve creates heterogeneity of repolarization, which contributes to AF.

The present study also showed that dronedarone produces a reduction in heart rate in anesthetized dogs both at baseline (before the onset of RAP) and after RAP with PE infusion (2 μg/kg/min). This effect was consistent with our previous study in isoflurane-anesthetized dogs and in conscious dogs instrumented with telemetry units [31]. The efficacy of dronedarone in reducing the ventricular rate was also observed in patients with permanent AF both at rest and during exercise [10]. It has been shown previously that dronedarone exerts a bradycardia effect with different combinations of inhibition of pacemaker current and blockade of β-adrenergic receptor and calcium channels [4, 8, 13, 29]. Heart rate reduction is the therapeutic target in patients with heart disease, including patients with AF, since an elevated HR results in increased myocardium oxygen demand and energy depletion, which aggravates heart function. Therefore, the reduction of HR and VR caused by dronedarone in

AF dogs might preserve the cardiac function and reduce the risk of development of congestive heart failure.

Dronedarone has been reported to prevent and terminate AF in previous *in vitro* models [6, 7]. In canine isolated arterially perfused right atria, acute dronedarone (10 μM) prevents acetylcholine-mediated AF and terminates persistent AF [6]. Furthermore, a combination of dronedarone (10 μmol/l) and ranolazine (5 μmol/l) has been shown to prevent the induction of AF in canine isolated coronary-perfused right and left atria [7]. In this study, AF was induced in all dogs before receipt of dronedarone. After treatment, dronedarone was shown to reduce the duration of AF in 5 of 6 dogs in which one of those 5 dogs was unable to induce AF at all. Thus, our data on the management of AF are generally consistent with those reported previously. The mechanisms by which dronedarone reduced the duration of sustained AF in our study may be due to its effects on the APD of the atria and its effects on the AERP. In this study, dronedarone increased atrial APD 19.3%, which was less than its effect on the AERP (increased 23.1%), so PRR developed. The development of PRR was inconsistent with a previous study [7]. In canine right atrial preparations, dronedarone has been shown to alter the aAPD minimally, while its effect on the AERP was markedly lengthened, leading to development of PRR [7]. Bogdan and colleagues [4] suggested that dronedarone exhibits PRR by the state-dependent blockage of fast Na^+ channels in which a marked inhibition happens at a more depolarized holding potential. This effect could imply that dronedarone possesses an atrial-selective effect. It has been known that atrial cells have intrinsically a more depolarized resting membrane potential (RMP) than ventricular cells [3, 5]. Furthermore, when the shape of the aAPD is compared with the shape of the ventricular APD, the aAPD has slow phase 3 repolarization; therefore, atrial Na^+ channels will rest in the inactivated state for a longer time than ventricular Na^+ channels [4]. Dronedarone and amiodarone, a structurally related compound, have been demonstrated to preferentially block Na^+ channels in an inactive state [11]. A previous study also showed that a multichannel blocking drug like amiodarone but not a pure potassium channel blocker like *d*-sotalol suppressed excitability during the late repolarization phase in humans [12]. Studies of Maruyama and colleagues (1995) and Kirchhof *et al.* (2003) have also supported that the additional sodium blocking effect of amiodarone might be responsible for PRR [19, 22].

Study limitations

All investigations of the present study were performed in anesthetized healthy dogs. In clinical practice, however, dogs with AF almost always have underlying heart diseases. Therefore, extrapolations of results obtained from this study to the clinic should be done with caution.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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