Chronic Effect of Oral Dronedarone Administration on Electrocardiography, Hemodynamic, and Cardiac Function in Conscious, Telemetry Dogs

N. Saengklub¹, C. del Rio², A. Kijtawornrat¹ 4*
¹Graduate Student in the Program of Animal Physiology, Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand
²QTest Labs, LLC., OH, USA
³Department of Physiology, Faculty of Veterinary Science
4Research study and testing of drug’s effect related to cardiovascular system in laboratory animal research clusters, Chulalongkorn University, Bangkok, Thailand
*Corresponding author: kanusak@hotmail.com

Keywords: cardiac function, chronic, dog, dronedarone, oral, telemetry

Introduction
Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by irregularly rapid atrial activity. In canine, AF most commonly develop in association with structural or functional heart diseases such as dilated cardiomyopathy (DCM) and acquired valvular disease especially mitral valve (1, 8). Dronedarone is an antiarrhythmic drug widely used for treatment of atrial fibrillation (AF) and ventricular arrhythmias in both humans and experimental animal models (4, 5). It possesses multi-channel blocker and adrenergic receptor blocker. Dronedarone was extensively metabolized in dog to form SR35021 and SR90154 and was excreted primarily via feces. Chronic oral administration of dronedarone (10 and 30 mg/kg, bid, 1 week) has been shown to prevent ventricular fibrillation (VF) induced by a sympathetic hyperactivity in a healed myocardial infarction dog (3). In canine model of chronic atrioventricular block, dronedarone (20 mg/kg, bid, 3 weeks) increased QT interval (8). On the other hand, dronedarone (25 mg/kg, bid, 4 weeks) did not alter QT and QTc intervals (6). Furthermore, dronedarone (10 and 30 mg/kg, bid, 1 week) did not change mean arterial pressure, dP/dt max, fractional shortening and ejection fraction in dog with healed myocardial infarction (3). All of these results led to unreliable conclusion and the extensive experiment is needed to warrant the effects of oral dronedarone in conscious dog. Dog telemetry model has been validated for sensitivity and specificity recently and used extensively for monitoring electrocardiogram, blood pressure, and left ventricular pressure simultaneously (2). This study aimed to continuously monitor cardiovascular responses after chronic administration for 7 days in conscious dog with telemetry unit implanted.

Materials and Methods
Four healthy mature Beagles of either gender were surgically implanted with a Data Sciences International radiotelemetry transmitter (TL11M3-D70-PCTP (4 dogs)), which has systemic arterial blood pressure (systolic, diastolic, and mean), heart rate, ECG, and body temperature data collection capabilities. The PCTP transmitter also has left ventricular pressure data collection capabilities. All dogs were received oral doses dronedarone at 20 mg/kg bid for 7 days (3, 7). Telemetric device was programmed using the Dataquest ART 3.1 software to record electrocardiograms, blood pressure, body temperature, left ventricular pressure data, and pressure-volume relationship data. Standard ECG intervals (RR, PQ, QRS, and QT) were manually measured by using ECG auto software (EMKA Technologies, VA, USA). A mean of the averaged 30 seconds per time-point was reported. The QT interval was corrected for heart rate (QTc) by using Fridericia formula. Contractility index (CI), relaxation time (RT), dP/dt max, and dP/dt min were calculated from LVP data. End systolic pressure-volume relationship (ESPVR), end diastolic pressure-volume relationship (EDPVR), and preload recruitable stroke work (PRSW) were obtained from pressure-volume relations. All data were monitored at baseline, every hour (at 4 to 8 hours), day 4, and day 7. Statistical analysis was performed using one-way analysis of variance (ANOVA) for multiple groups or followed by Dennett’s multiple comparison, as appropriate. All data are expressed as mean ± SEM.

Results and Discussion
Electrocardiographic parameters
PR interval showed a peak of significantly decreased at day 4 (p < 0.001) but less significantly decreased at day 7 (p < 0.001) (Fig 1a). QT interval tended to continuously increased and peaked at day 4 (Figure 1b). HR, RR interval, QRS and QTc(f) interval were not significantly changed (data not shown).

Left ventricular pressure analysis
CI tended to increase at day 7. RT tended to decrease at 8 hr. dP/dt max, and dP/dt min were not significantly changed (data not shown).

Analysis of pressure-volume relations
ESPVR, EDPVR, and PRSW were not significantly changed (data not shown).

In conclusion, chronic dronedarone administration for 7 days in conscious dog has no effect on hemodynamic and cardiac function of the dogs while...
it tended to lengthen QT interval and significantly prolonged PR interval. This could be explained by the multichannel blocking properties of the dronedarone especially the calcium channel blocking effect.

Figure 1 shows a) PR interval and b) QT interval in response to chronic oral dronedarone administration (20 mg/kg bid 7 days). ** indicates \( p < 0.001 \)

Acknowledgements
The authors would like to thank QTTest Labs, LLC for financial support and place for study. The authors also would like to thank H.M. King Bhumibol Adulyadej’s 72nd Birthday Anniversary Scholarship, Graduate School, Chulalongkorn University and Ratchadapiseksomphot Endowment Fund (GSTAR 56-008-31-001), Chulalongkorn University.

References