



# EFFECT OF FLECAINIDE AND DRONEDARONE ON ATRIAL AND VENTRICULAR EFFECTIVE REFRACTORY PERIOD IN THE DOG WITH PACING INDUCED ATRIAL REMODELING

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## BACKGROUND

Atrial fibrillation occurs in 4.5 million Europeans, putting them at risk of stroke and clots.

- Animal models of atrial fibrillation (AF) usually focus on acute, anesthetized paradigms or complex electrophysiology assessments not particularly suited for efficacy examination with multiple compounds.
- The industry continues to look for robust, relevant nonclinical models of atrial and ventricular electrophysiology to examine new molecular entities for efficacy in this therapeutic area.

## PURPOSE

The objective of this study was to interrogate the selectivity of flecainide and dronedarone on atrial and ventricular effective refractoriness using a chronic model of atrial remodeling in the conscious dog. Previously we demonstrated that rapid atrial pacing for at least two weeks was associated with shortening of atrial effective refractory period (AERP) along with inducible periods of atrial fibrillation.

- Parameters obtained included
  - Threshold capture voltage
  - AERP (500, 400, 300 msec)
  - VERP (500, 400, 300 msec)
  - PK sampling

## MATERIALS AND METHODS

### Experimental Preparation

Male Beagle dogs (n=5, 8-11 kg each) were surgically instrumented with telemetry devices to monitor blood pressure, heart rate, and electrocardiogram. During this instrumentation, two sets of bipolar electrodes were placed on both the right atrium and right ventricular outflow tract with externalization of the electrode wires. These electrodes were subsequently used for chronic pacing and weekly determination of atrial and ventricular effective refractory periods. After two weeks of recovery, atrial pacing was initiated at 400 bpm continuously.

During the period of continuous high rate atrial pacing, AERP progressively decreased while VERP remained at pre-pacing levels. Atrial fibrillation could also be induced via the use of atrial burst pacing after approximately 2-3 weeks. At this point, dogs were randomized to receive vehicle, flecainide, and dronedarone in a crossover paradigm. Each cohort received compound as an escalating dose regimen with each dosing epoch consisting of 10 minutes loading dose followed by 40 minutes of maintenance dose (or matched vehicle controls). Electrophysiological assessments were performed during the maintenance periods of each dosing epoch.

### Atrial Effective Refractory Period

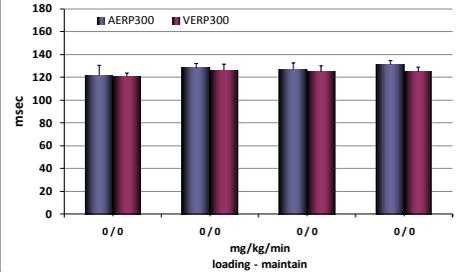
For determination of atrial effective refractory period (AERP), hearts experienced cycles of 8 paced beats of atrial origin ( $S_1$ ) at twice electrical diastolic threshold, using three discrete fixed cycle length (500, 400, and 300 ms) followed by an extra atrial stimulus ( $S_2$ ) delivered at varying 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.

### Ventricular Effective Refractory Period

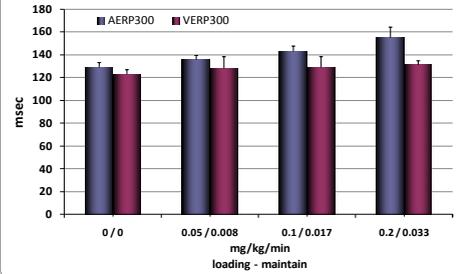
For determination of ventricular effective refractory period (VERP), hearts experienced cycles of 8 paced beats of ventricular origin ( $S_1$ ; at twice electrical diastolic threshold, using three discrete fixed cycle lengths) followed by an extra ventricular stimulus ( $S_2$ ) delivered at varying coupling intervals from the eight beat train of  $S_1$  initiating during the maintenance dosing period. The  $S_2$  coupling time that failed to elicit a ventricular response as determined by inspection of the ECG will be noted as the VERP. The  $S_2$  coupling interval started short and was lengthened until capture was noted.

## RESULTS

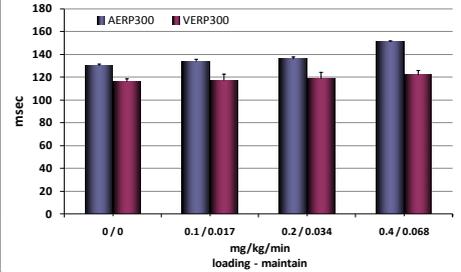
Electrophysiological Effects of Vehicle in Conscious Telemeterized Male Beagle Dogs  
AERP vs VERP



Electrophysiological Effects of Flecainide in Conscious Telemeterized Male Beagle Dogs  
AERP vs VERP



Electrophysiological Effects of Dronedarone in Conscious Telemeterized Male Beagle Dogs  
AERP vs VERP



## CONCLUSION

In summary, a model of atrial remodeling following chronic high-rate pacing was used to interrogate the atrial selectivity and dose-response of marketed anti-arrhythmics in the conscious dog. Dose-dependent prolongations of AERP, but not VERP, were observed with flecainide and dronedarone. This model possesses utility as a paradigm to determine the differential efficacy of test articles on atrial and ventricular refractoriness.