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## CARDIAC ARRHYTHMIAS

**EFFECTS OF K201 ON REPOLARIZATION AND ARRHYTHMOGENESIS IN DOGS WITH CHRONIC COMPLETE ATRIOVENTRICULAR BLOCK**

ACC Poster Contributions

Ernest N. Morial Convention Center, Hall F

Sunday, April 03, 2011, 3:30 p.m.-4:45 p.m.

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Session Title: Electrophysiology -- Basic. Effects of Biologically Active Agents and Arrhythmias on Cardiac Electrophysiology

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**Background:** The new antiarrhythmic drug K201 is currently in development for treatment of atrial fibrillation. K201 controls intracellular calcium release by the ryanodine receptors, but also has a ventricular class III action that might predispose to Torsade de Pointes (TdP) arrhythmias. In this study anti- and proarrhythmic effects of K201 were investigated at two doses in dogs with chronic complete atrioventricular block (CAVB) susceptible to dofetilide-induced TdP.

**Methods:** Under general anesthesia two doses of K201 (0.1 and 0.3 mg/kg/2 min followed by 0.01 and 0.03 mg/kg/min for 30 min intravenously, respectively) were tested serially in normal sinus rhythm dogs (n=10) and CAVB dogs. TdP-susceptibility was assessed with dofetilide (0.025 mg/kg/5min intravenously). In susceptible dogs, K201 was administered in 3 serial experiments, after dofetilide (n=8) and before dofetilide (n=7 for either dose). Beat-to-beat variability was quantified as short-term variability of left ventricular monophasic action potential duration (STV). A pacing protocol was included to increase sensitivity of the model to TdP.

**Results:** In normal sinus rhythm dogs both doses of K201 prolonged ventricular repolarization whereas only the higher dose prolonged atrial repolarization. At CAVB, dofetilide induced TdP in 9 of 10 dogs preceded by an increase in STV. K201 did not suppress dofetilide-induced TdP. Administered before dofetilide, K201 dose-dependently prolonged ventricular repolarization. The lower dose did not induce TdP and did not increase STV (from 1.0±0.5 to 1.3±0.7 ms, p=NS) whereas the higher dose increased STV (from 1.2±0.4 to 2.9±0.8 ms, p<0.05) and resulted in spontaneous repetitive TdP in 1 dog; with inclusion of the pacing protocol TdP-inducibility increased to 3 of 7 dogs (vs. 0 of 7 at baseline, p=NS). No preventive effects against dofetilide-induced TdP were seen at either dose.

**Conclusions:** Both doses of K201 showed a class III effect. In TdP-sensitive CAVB dogs no relevant antiarrhythmic effects against dofetilide-induced TdP were seen. Only at the higher dose a proarrhythmic signal was observed preceded by an increase in STV. This indicates a small safety margin.