INTRAVENOUS INFUSION OF THE BETA-3 ADRENERGIC RECEPTOR ANTAGONIST APD418 IMPROVES LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION IN DOGS WITH HEART FAILURE: A SINGLE DOSE, 6 HOURS STUDY

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Abstract:
Background: The β_3-adrenergic receptor was initially identified in fat and subsequently found in the myocardium. Unlike β_1 and β_2-adrenergic receptors, β_3 receptor stimulation inhibits cardiac contraction and relaxation through its link to inhibitory G proteins (Gi). Stimulation of cardiac β_3 receptors has been shown to have a negative effect on the cardiac contractile state without eliciting direct chronotropic effects. In the failing left ventricular (LV) myocardium, β_3-adrenergic receptors are upregulated, a maladaptation that can contribute to LV systolic dysfunction characteristic of the heart failure (HF) state. This study examined the effects of a single dose, 6 hours intravenous infusions of the β_3-adrenergic receptor antagonist APD418 on LV systolic and diastolic function in dogs with HF (LV ejection fraction, EF~35%). Methods: Studies were performed in 7 dogs with coronary microembolizations-induced HF. Dogs were randomized to receive a 6 hour infusion of APD418 (4.224 mg/kg) or a 6 hour infusion of 0.9% NaCl (vehicle) administered 1 week apart. Hemodynamic, ventriculographic and echocardiographic-Doppler measurements were made at baseline and at 2 and 6 hours after administration of APD418 or vehicle. Heart rate (HR), mean aortic pressure (mAoP), LV end-diastolic (EDV) and end-systolic (ESV) volumes, EF, cardiac output (CO), systemic vascular resistance (SVR) and myocardial oxygen consumption (MVO_2) as well as the diastolic function measures Ei/Ai and mitral inflow velocity deceleration time (DCT) were measured at each time point. Results: Infusion of vehicle for 6 hours had no significant effects on any of the ventriculographic and echocardiographic-Doppler measures but caused lowering of mAoP and SVR likely due to duration of infusion under general anesthesia. Infusion of APD418 had no significant effects on HR, mAoP, EDV or MVO_2, decreased ESV, significantly decreased SVR and significantly increased EF, CO, Ei/Ai and DCT (Table). Comparison of treatment effect Δ (change between baseline and 6 hours) between vehicle and APD418 showed that APD418 significantly decreased ESV, and significantly increased EF, SV, CO, Ei/Ai, mAoP and DCT with no changes to EDV, HR, and SVR (data not shown). Conclusions: The results of the study indicate that 6 hours intravenous infusions of APD418 in dogs with systolic HF elicit positive inotropic and lusitropic effects. The data support the continued development of APD418 for the treatment of patients with HF.

Table: Hemodynamic, ventriculographic and 2-D echocardiographic/Doppler measures

	VEHICLE			APD418		
	Baseline	2 Hours	6 Hours	Baseline	2 Hours	6 Hours
EDV (ml)	57±5	57±5	56±4	59±4	59±4	59±4
ESV (ml)	39±3	39±3	30±3	40±3	39±3	37±3
EF (%)	32±1	32±1	32±1	31±1	35±1*	38±1*
SV (ml)	18±1	18±2	18±2	18±1	21±1*	22±1*
CO (L/min)	1.47±0.13	1.47±0.14	1.49±0.13	1.46±0.10	1.65±0.14*	1.77±0.12*
HR (beats/min)	82±2	80±2	82±2	79±2	80±2	80±3
mAoP (mmHg)	75±1	70±1*	66±1*	70±2	71±2	67±1
SVR (dynes-sec-cm^{-5})	4287±467	4045±453*	3755±409*	3948±317	3585±292*	3123±229*
MVO_2 (μmoles/min)	122±20	106±10	119±19	138±17	134±14	151±15
Ei/Ai	3.3±0.3	3.5±0.3	3.6±0.4	3.4±0.4	3.9±0.5*	4.9±0.5*
DCT (msec)	134±4	137±4	138±5	119±7	128±6	144±8*
*=p<0.05 vs. Baseline						