Vasomera™, a Novel VPAC2-Selective Vasoactive Intestinal Peptide Agonist: Enhanced Contractility and Decreased Myocardial Demand in Dogs with both Normal Hearts and with Pacing-Induced Dilated Cardiomyopathy.

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Introduction

The natural vasoactive intestinal peptide (VIP) has been proposed as a therapeutic agent for heart failure via the activation of the G-protein-coupled VPAC1 and VPAC2 receptors; however, VIP's clinical utility is limited due to its short half-life and VPAC1-mediated side-effects. Vasomera™ (PB1046) is a novel long-acting biopolymer-based selective VPAC2-receptor agonist.

This study evaluated the acute cardiovascular profile of PB1046 when administered as an IV escalating dose infusion in dogs, both normal and with pacing-induced systolic dysfunction (DCM) mimicking the clinical manifestation(s) of the heart failure (HF) syndrome. In particular, this study determined the dose response and no-effect levels of PB1046 on load-independent left-ventricular (LV) mechano-energetic parameters via pressure-volume (PV) curve analyses.

Materials and Methods

Beagle dogs (n = 10) were instrumented, chronically and/or acutely (i.e., terminally under anesthesia), for the determination of LV hemodynamics, cardiac-output (CO), and load-independent LV inotropy/lusitropy via pressure-volume relationships. A subset of dogs (DCM, n = 6) also had heart failure induced (prior to enrollment in the studies) via orthodromic right-ventricular pacing, as documented via both echocardiographic (LVIDd: +9 ± 3%, EF: -35 ± 2%, P < 0.05) and neurohumoral changes (NT-proBNP: 413 ± 53 to 2394 ± 331 pM/L, P < 0.05) consistent with HF.

In all cases, the effects of PB1046 (0.03 to 100 µg/kg/min IV, ~20min/dose) on LV mechno-energetics were evaluated, either under anesthesia (isoflurane; n = 8) and/or conscious (n = 2 DCM). Data are presented as means ± SEM, with a significance level of P < 0.05 (ANOVA).

Results

PB1046 plasma concentrations increased with the rate of administration, reaching detection levels (i.e., > 19.5 ng/mL) at rates/doses of at least 1 µg/kg/min (see Fig.1). Negligible hemodynamic/functional effects of PB1046 were noted at the 0.01 µg/kg/min (e.g., CO: 1 ± 4%, 1.8 ± 0.2 to 1.8 ± 0.0 L/min, Ea: -5 ± 1%, 4.3 ± 0.1 to 4.1 ± 0.1 mmHg/mL, and PRSW: 0 ± 1%, 92 ± 6 to 92 ± 5 mmHg*) while notable (and expected) adverse gastrointestinal reactions (watery diarrhea/vomiting) were noted at doses of 30 to 100 µg/kg/min (reaching 18,200 ± 1.249 ng/mL at 30 µg/kg/min). Within the 0.03 and 1 µg/kg/min dose-range (reaching 448 ± 56 ng/mL, PB1046 tended to moderately decrease LV end-systolic pressures, while triggering dose-dependent reductions in arterial elastance (Ea) and notable positive inotropy (see Fig. 2 top).

At 0.1 µg/kg/min (36 ± 6 ng/mL), PB1046 decreased Ea by 15 ± 2% (5.8 ± 0.7 to 5.0 ± 0.5 mmHg/mL, P < 0.05) while leading to steeper ESPVR (+18 ± 2%, 4.4 ± 0.9 to 5.0 ± 1.1 mmHg/mL, P < 0.05) and PRSW (+15 ± 3%, 67 ± 7 to 77 ± 7 mmHg*, P < 0.05) slopes, suggesting improved ventriculo-arterial coupling/performance (Ea/Es). Similarly, the slope of the EDPRV decreased post-dosing (e.g., 0.9 ± 0.2 to 0.7 ± 0.2 mmHg/ml at 0.1 µg/kg/min, P < 0.05), suggesting improved lusitropy.

Concomitantly, PB1046 dose-dependently increased cardiac output despite minimal/unchanged chronotropy; for instance, at 0.1 µg/kg/min CO increased by 13 ± 2% (1.4 ± 0.1 to 1.6 ± 0.1 L/min, P < 0.05) while heart rate changed negligibly (99 ± 4 to 97 ± 5 bpm, N.S.).

Notably, the LV pressure-volume area (PVA) decreased significantly with PB1046 treatment (e.g., at -20 ± 3% at 0.1 µg/kg/min, 3.9 ± 6.0 to 3.0 ± 0.5 mmHg*L, P < 0.05), suggesting preserved/decreased myocardial oxygen demand.

The effects of PB1046 were noted in both normal and DCM dogs (see Fig. 2 bottom), as well as in conscious animals free of concomitant anesthetic effects. For instance, in two conscious DCM dogs, PB1046 (at 0.1 µg/kg/min) decreased arterial elastance (Ea: -16 and -19%) and increased the PRSW slope (+25 and +11%) with negligible effects on heart rate (HR: -9 and -2%).

Conclusion

Vasomera, a novel VPAC2 agonist, when given as a continuous intravenous infusion decreased myocardial loading and improved myocardial energetics, while improving both systolic and diastolic function in a load-independent manner when given as a continuous intravenous infusion. These salutary effects were noted, free of adverse effects, within the 0.1 to 1 µg/kg/min dose-range, in dogs with both normal and dysfunctional ventricles.