Vasomera™, a Novel VPAC2-Selective Vasoactive Intestinal Peptide Agonist:

Improved Ventriculo-Arterial Coupling and Decreased Myocardial Demand in Sheep with Induced Ischemic Heart Failure.

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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-eceptor agonist, which may circumvent the limitation(s) of traditional VIP agonists. This study evaluated the cardiovascular profile of PB1046 when administered as an IV escalating dose infusion in animals with normal and dysfunctional left ventricles (LV).

In particular, the acute effects of Vasomera in load-independent function and ventriculo-arterial coupling (via LV pressure-volume analyses) were determined in sheep with failing ischemic ventricles mimicking the clinical manifestation(s) of the heart failure (HF) syndrome.

Materials and Methods

Mixed-breed (Dorset-mixed; n = 10, 64.7 ± 3.2 kg) sheep were instrumented for the determination of systemic/left-ventricular hemodynamic as well as for the evaluation of cardiac-output (via thermo-dilution), load-independent left-ventricular (LV) inotropy/lusitropy and ventriculo-arterial coupling (via pressure-volume relationships), as well as for the assessment of myocardial oxygen extraction. A subset of animals (n = 5, 51.3 ± 2.1 kg) had heart failure induced (prior to instrumentation) via serial (weekly) coronary embolizations, resulting in depressed LV function (EF: 28 ± 1%) and elevated filling pressures (EDP: 22 ± 2mmHg).

In all cases, the effects of PB1046 (0.03 to 10 µg/kg/min IV, ~20min/dose) on LV mechano-energetics were evaluated under anesthesia (isoflurane) in either healthy (n = 5, CTRL) or failing sheep (HF, n = 5). Data are presented as means ± SEM, with P < 0.05 (ANOVA).

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Results

In HF sheep, Vasomera decreased the estimated arterial elastance (Ea: -24 ± 5%, 2.3 ± 0.2 to 1.9 ± 0.9 mmHg/mL, P < 0.05) with negligible changes in heart rate (114 ± 4 to 111 ± 6 bpm) (see Fig. 1). Steeper ESPVR (Ees: 1.2 ± 0.1 to 1.9 ± 0.2 mmHg/mL, P < 0.05) and PRSW slopes (45 ± 4 to 61 ± 7 mmHg*, P < 0.05) were observed post-treatment, suggesting positive (load independent) inotropy and improved ventriculo-arterial coupling (Ea/Ees: 2.0 ± 0.3 to 1.1 ± 0.2, P < 0.05). Moreover, PB1046 markedly improved compliance (EDPVR: 1.9 ± 0.4 to 0.6 ± 0.1 mmHg/mL, P < 0.05) in failing hearts.

Concomitantly, cardiac output (CO: 4.3 ± 0.2 to 4.9 ± 0.4 L/min, P < 0.05) increased while myocardial oxygen extraction decreased (O2ex: 41 ± 5 to 20 ± 4%, P < 0.05); the LV pressure-volume area, a correlate of myocardial demand, also decreased (PVA: 15.3 ± 2.2 to 6.0 ± 1.0 mmHg*L, P < 0.05).

In healthy sheep, PB1046 had comparable mechano-energetic effects (see Fig 1). Overall, plasma concentrations increased with the rate of administration. At 0.3 µg/kg/min, sheep reached a plasma concentration of 116 ± 5 ng/mL. All dose-levels assayed were well tolerated (35 ± 5 to 4,640 ng/mL(at 0.03 and 10 µg/kg/min, respectively).

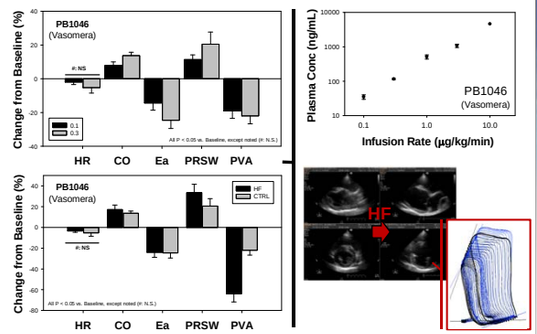

Fig. 1. LEFT: Acute Effects of PB1046 (IV, ~20min/dose) in sheep; RIGHT: plasma concentrations (top), and representative ECHO/PV loops (bottom)

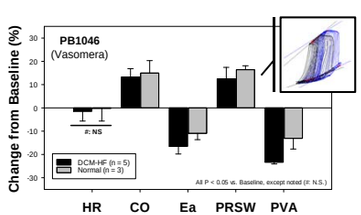

Fig. 2. Acute Effects of PB1046 (IV infusion) in dogs

In dogs, PB1046 triggered similar dose-dependent reductions in arterial elastance (Ea) and positive inotropy (see Fig. 2). 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 %, 62 ± 7 to 67 ± 10 mmHg*, P < 0.05) slopes. PB1046 also dose-dependently increased cardiac output despite minimal/unchanged chronotropy (e.g., at 0.1 µg/kg/min, CO increased by 13 ± 2%, form 1.4 ± 0.1 to 1.6 ± 0.1 L/min, P < 0.05). Notably, the LV pressure-volume area (PVA) also decreased significantly with PB1046 treatment (e.g., at -20 ± 3% at 0.1 µg/kg/min, 3.9 ± 0.6 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.

Conclusion

Vasomera, a novel VPAC2 agonist, when given as a continuous IV infusion decreased myocardial loading and myocardial demand, while improving both load-independent LV function (systolic/diastolic) and ventriculo-arterial coupling in the setting of ischemic heart failure. These salutary effects have been noted, free of adverse effects, within the 0.1 to 1 µg/kg/min dose-range, in animals with both normal and dysfunctional ventricles.

In collaboration with:

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