Vasomera™, A Novel VPAC2-Selective Vasoactive Intestinal Peptide Agonist

Evidence for Chronic Cardio-Protection in Rats with Doxorubicin-Induced Cardiomyopathy.

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Introduction

The natural vasoactive intestinal peptide (VIP) has been proposed as a therapeutic agent for heart failure triggering potent vasodilatation/inotropy via the activation of the G-protein-coupled VIPAC1 and VPAC2 receptors; however, VIP's clinical utility is limited due to its short half-life and VPAC1-mediated side-effects.

PhaseBio’s novel ELP fusion technology (ELP+) permits the creation of long-acting protein-fusion biopolymer-based VPAC-receptor agonists. Vasomera™ (PB1046) is a novel long-acting biopolymer-based, ELP fusion, selective VPAC2-receptor agonist. Here, the chronic functional/geometrical effects of Vasomera were evaluated when given daily to rats with doxorubicin-induced cardiomyopathy.

Vasomera, a novel ELP-enhanced VPAC2 agonist, can trigger salutary effects in the setting of induced cardiomyopathy.

Results

Doxorubicin lead to marked LV dysfunction/remodeling, characterized by depressed systolic function (e.g., FS, -18 ± 4 %, P<0.05), myocardial dilatation (e.g., LVIDd: -12 ± 2, P<0.05), and wall-thinning (WT: -15 ± 5 %, P<0.05).

Daily Vasomera therapy prevented doxorubicin-induced myocardial wasting/wall-thinning (WTs: +1 ± 4 %, N.S.), ameliorating ventricular dysfunction (e.g., FS, -8 ± 2 %, P<0.05) and dilatation (LVIDd: +3 ± 3, N.S.). Vasomera treatment also tended to preserve the LV- to-body-weight ratio (-2.4 ± 2.0 % vs. time-controls, N.S.), when compared to un-treated animals (-7.5 ± 3.0 % vs. time-controls, P = 0.1). Terminally, Vasomera-treated animals tended to have lower LV filling pressures (EDP: 13 ± 1 vs. 9 ± 1 mmHg).

Vasomera dose-dependently decreased arterial and LV end-systolic/filling pressures and arterial-elastance. At 7.5 µg/kg/min (IV) steeper ESPVR (+17 ± 6 %, 23 ± 2 to 27 ± 2 mmHg/RVU, P<0.05) and PRSW (+18 ± 3 %, 46 ± 2 to 54 ± 3 mmHg*, P<0.05) slopes were observed. Concomitantly, the slope of the EDPVR decreased 20 ± 3 % (2.6 ± 0.2 to 2.0 ± 0.1 mmHg/RVU, P < 0.05) (see Fig. 2).

Both LV stroke-work (SW: 191 ± 13 to 164 ± 13 mmHg*RVU, P<0.05) and LV pressure-volume area (PVA: 563 ± 35 to 415 ± 29 mmHg*RVU, P<0.05) were decreased by Vasomera.

In SHR rats, Vasomera induced dose-dependent blood pressure decreases that were sustained for up to 12 hours post-dosing (see Fig. 3A-B). At 9 mg/kg, Vasomera lowered MAP by 9 ± 1 % (188 ± 6 to 171 ± 5 mmHg, P<0.05), with a peak reduction of 16 ± 3 % (154 ± 5 mmHg vs. 184 ± 6 in VEH, P<0.05) observed -6 hr post-dosing (see Fig. 3A). PB1046 also triggered moderate (dose-dependent) cardiac-acceleration. At 9 mg/kg, for example, heart rate increased +8 ± 1 % (355 ± 6 to 384 ± 8 bpm, P<0.05) after administration; however, no significant cardio-acceleration was observed at the lowest dose level assessed (356 ± 5 to 362 ± 5 bpm).

Nonetheless, despite the increased HR, the rate-pressure product was unaffected (e.g., at 9 mg/kg, -2 ± 1 %, from 67 ± 2 to 68 ± 2 mmHg*bps x 10^3).

Conclusion

Daily treatment with Vasomera, a novel VPAC2 agonist, attenuated doxorubicin-induced myocardial remodeling/dysfunction in rats. In particular, Vasomera treatment prevented myocardial wall-thinning/muscular wasting. Moreover, acute Vasomera administration (IV) to rats with doxorubicin-induced cardiomyopathy, dose-dependently decreased myocardial loading and energetic demand, while improving LV systolic/diastolic function in a load-independent manner.