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 VPAC1 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 .

Materials and Methods

Rats (SD, 233 ± 2 g, n = 46) were assigned to receive daily therapy with either Vasomera (9 mg/kg/day SQ; n = 23) or placebo (n = 23); one subset of rats from each group (HF, n = 27) had heart failure induced via doxorubicin (3 mg/kg IP; 18 mg/kg total), while another served as controls (SHAM, n = 19); daily treatments started prior to HF induction (5 days) and continued until the end of the study. LV function/geometry were evaluated (via echo) prior to the start of dosing, as well as weekly both during/after (for up to 3 weeks) HF induction. LV hemodynamics and mechano-energetics (pressure-volume relationships) were terminally studied in response to escalating doses of Vasomera (1, 2.5 and 7.5 µg/kg/min IV).

The hemodynamic effects of Vasomera (1 to 9 mg/kg SQ) were evaluated in conscious telemetered SHR rats (351 ± 4 g, n = 8) either untreated or during β-AR blockade (+BB, atenolol 20 mg/kg), calcium-channel blockade (+CCB, amlodipine 5 mg/kg), and ACE-inhibition (+ACE, ramipril 1 mg/kg).

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).

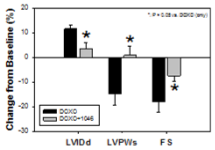

Fig. 1. Vasomera (PB1046) attenuated doxorubicin-induced LV remodeling.

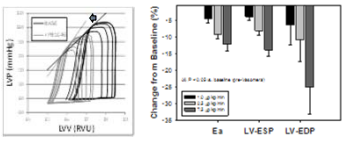

Fig. 2. (right) Effects of Vasomera on LV loading conditions; (left) Representative LV pressure-volume loops before/after Vasomera.

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.

Long-Term Hemodynamics

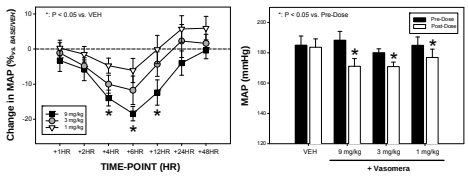

Fig. 3. Changes in mean arterial pressure (MAP) following a single-dose (SQ) administration of either three dose levels of Vasomera (1, 3, and 9 mg/kg) or vehicle (VEH) in untreated SHR rats.

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) cardio-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 66 ± 2 mmHg*bpm x 10^3).

Vasomera's induced vaso-relaxation was preserved in rats pre-treated with either atenolol (+BB: -14 ± 1%, P<0.05), amlodipine (+CCB: -13 ± 2%, P<0.05) and/or ramipril (+ACE: -9 ± 2%, P<0.05) (see Fig. 4, left); similar results were observed in animals pretreated with a diuretic (-8 ± 0%, P<0.05).

On the other hand, chronotropy seemed to be blunted under β-AR blockade (+6 ± 1%, 278 ± 2 to 294 ± 2 bpm), but was unaffected by amlodipine, ramipril, or hydrochlorizide (see Fig. 4, right). In all cases, no adverse clinical effects and/or drug-to-drug interactions were noted.

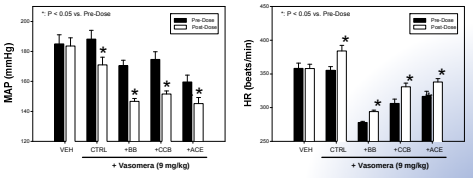

Fig. 4. Changes in mean arterial pressure (MAP) and heart rate (HR) following PB1046 administration (9 mg/kg, SQ) in pre-treated SHR rats.

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.