Evaluation of Vasomera™, A Novel VPAC2-selective VIP Agonist, on Telemetered SHR Rats:

Evidence for Dose-dependent Sustained Blood Pressure Control Independent of β-AR Function.

del Rio CL[1], Georgopoulos L[2], Arnold S[2], Brown T[1], Wallery J[1], Hamlin RL[1,3].

1: QTest Labs; OH (USA). 2: PhaseBio Pharmaceuticals, Inc, Malvern, PA (USA), and 3: The Ohio State University, OH (USA).

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Introduction

The natural vasoactive intestinal peptide (VIP) triggers potent vasodilatation by activating 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™ is a novel long-acting biopolymer-based selective VPAC2-receptor agonist. The main objective of these studies was to assess/establish the hemodynamic response(s) to Vasomera when given as a single subcutaneous (SQ) dose to conscious spontaneously hypertensive rats (SHR) receiving either no treatment (i.e., controls) or being pretreated with commonly used anti-hypertensive agents.

Vasomera can provide long-lasting reductions in blood pressure, independent of beta-adrenergic receptor function (β-AR).

Materials and Methods

SHR rats (351 ± 4 g, n = 8) were instrumented for telemetric blood pressure and ECG monitoring. First, via a Latin-Square design, the effects of three dose-levels of Vasomera (1, 3, and 9 mg/kg SQ) as well as of vehicle (VEH: normal saline, SQ) were assayed in untreated animals. Then, the effects of Vasomera (9 mg [177nmol]/kg, SQ) were tested during concomitant oral β-AR blockade (+BB, atenolol 20 mg/kg/day, n = 8), calcium-channel blockade (+CCB, amlodipine 5 mg/kg/day, n = 4), and ACE-inhibition (+ACE, ramipril 1 mg/kg/day, n = 4), as well as enhanced dieresis (+DIU, hydrochlorizide 50 mg/kg/day, n = 4).

Finally, the effects of repeated daily dosing with Vasomera (9 mg/kg SQ) were evaluated in a subset of untreated animals (controls, CTRL; n = 4). In all cases, mean pressure (MAP) and heart rate (HR) were measured/averaged for 24 hours both pre- and post-dosing.

Results

Hemodynamics: Vasomera induced dose-dependent blood pressure decreases that were sustained for up to 12 hours post-dosing (see 1A-1B). 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 ~6hr post-dosing (see 1A). Vasomera also triggered moderate (dose-dependent) cardio-acceleration (see 1C). At 9 mg/kg, for example, heart rate increased +8 ± 1% (355 ± 6 to 384 ± 8 bpm, P<0.05) after administration (see 1C); however, no significant cardio-acceleration was observed at the lowest dose-level assessed (356 ± 5 to 362 ± 5 bpm).

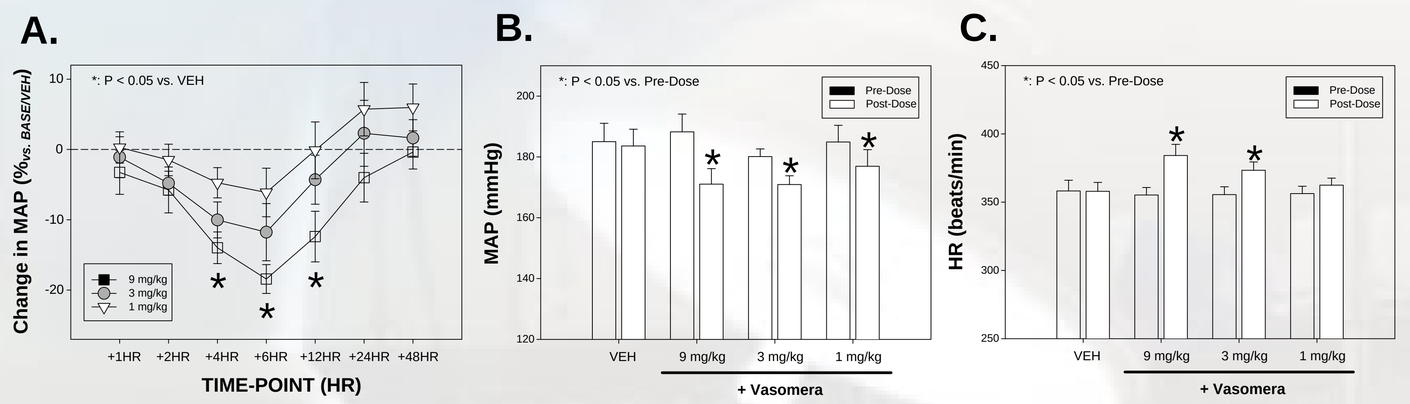

Fig. 1. Changes in mean arterial pressure (MAP) and heart rate (HR), following a single-dose (SQ) administration of either three dose-levels of Vasomera (1, 3, and 9 mg/kg) or vehicle (VEH) in untreated SHR rats.

Moreover, 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 x10^3)

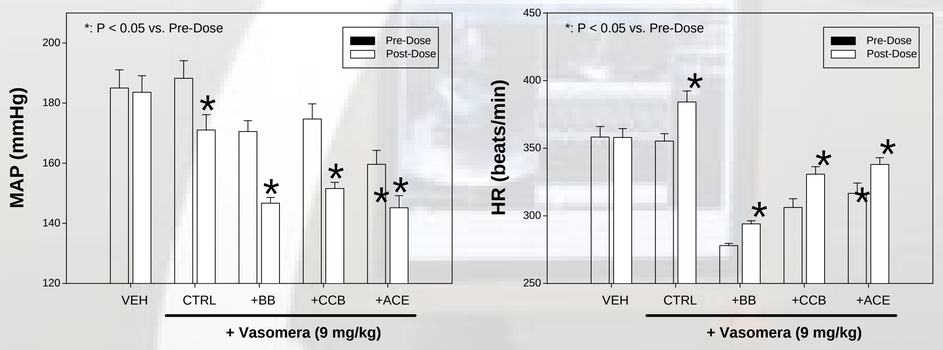

Fig. 2. MAP and HR after Vasomera in placebo-treated (CTRL), β-AR blocked (+BB), calcium-channel blocked (+CCB) and ACE-inhibited (+ACE) SHR rats.

Interactions: Vasomera's 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 2, 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 2, right). In all cases, no adverse clinical effects and/or drug-to-drug interactions were noted.

Repeated Dosing: On the first day of dosing, Vasomera triggered (as expected) marked blood pressure decreases (-11 ± 3%, 190 ± 7 to 169 ± 4 mmHg) and moderate cardio-acceleration (+11 ± 1%, 295 ± 5 to 327 ± 8 bpm, P < 0.05) (see 3). However, after daily administration (for 6 days), positive chronotropy was not observed (e.g., -2 ± 0%, from 296 ± 6 bpm on day 5 to 290 ± 5 bpm), while vaso-relaxation was preserved (e.g., -1 ± 1%, from 171 ± 5 mmHg on day 5 to 169 ± 4 mmHg on day 6), suggesting independent mechanisms for each response.

Moreover, in these animals, the QA interval, an index that (loosely) reflects the ventricular contractility, was preserved both on the first day of dosing (-1 ± 1%, 38 ± 1 to 38 ± 1 ms, N.S.) and at steady state (e.g., at day 6, +1 ± 1%, 39 ± 2 to 40 ± 2 ms, N.S.).

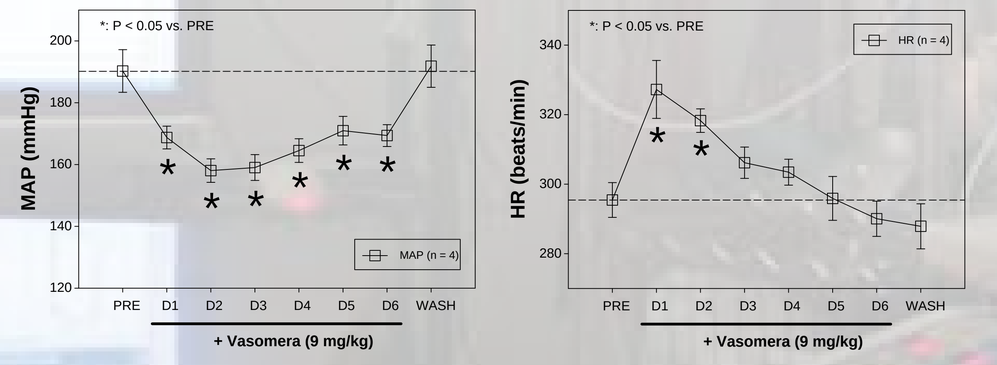

Fig. 3. MAP and HR following a 6-day single-dose (SQ) administration of Vasomera (9 mg/kg/day) in untreated SHR animals (n = 4).
NOTE: Data are 24hr-averages taken both pre-, during (daily, D1-D6), and post-dosing (WASH, 72hr after the last administration).

Pharmacokinetics: Plasma concentrations increased rapidly after-dosing; At 9 mg/kg, Tmax occurred at approximately 12 hours post-dose (~13,000 ng/mL, average) with levels gradually decreasing to ~80 ng/mL at 120 hours post-dose.

Conclusion

Vasomera, a novel VPAC2 agonist, provided long-acting blood pressure control synergistically with commonly-used concomitant anti-hypertensive therapies (e.g., β-AR blockade). Vasomera-induced vaso-relaxation was accompanied by a moderate cardio-acceleration that was transient in nature, but also tended to preserve myocardial performance and decrease demand; hence, Vasomera may represent a novel adjunct therapy for resistant/uncontrolled hypertension.

In collaboration with:

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