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Plasma Enalapril Kinetics of Two Modified Formulations Tested in Healthy Volunteers. A Pilot Trial Searching for an Optimum Blood Pressure Control.

Incardona C[1], Lombardo P[1], Feleder EC[2], Yerino GA[2], Halabe EK[2], Milei J[3], Ottaviano G[3], Muller A[3], Roldán EJ[1].

Author information

1 Medical Direction, Gador S.A., Buenos Aires, Argentina.
2 Clinical Research Unit, F.P. Clinical Pharma, Buenos Aires, Argentina.
3 Institute of Cardiological Research Prof. Dr. Alberto C. Taquini, Buenos Aires, Argentina.

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However, few data exist on central systolic and diastolic pressures (SBPC, DBPC) and arterial stiffness in these patients, and the effect of treatment on them. In this study we present the findings of a group of patients (P) receiving treatment established by their general practitioner.

Objectives: To assess the differences of the central pressure and pulse wave velocity (PWV) between men and women with IH with treatment prescribed by their general practitioner.

Materials and Methods: We studied 64 P with IH (mean age of 79 ± 6 years, 28 males and 36 females) receiving treatment since his family doctor in order to maintain BP below 140/80 mmHg. All of them submitted to a study of central pressures (SBPC, DBPC), PWV and the augmentation index (AI) to contrast the differences between the sexes. The results were compared and are shown in the following table:

Results

DATA	SBPc	DBPc	PWV	AI
Males	104±3	79±4	7±3	22±5
Women	122±4*	81±3	9±4	29±3*

*Denotes p <0.05.

Conclusions: According to our findings, having similar peripheral blood pressures, women have a SBPC significantly higher than that of men. Furthermore, arterial stiffness measured by the AI is significantly higher, giving to these patients a much higher risk than men of similar age and apparently good blood pressure control.

Keywords: isolate systolic hypertension, elderly, central pressures, arterial stiffness

ENDOTHELIAL FUNCTION

LB-P-07

Secreted Monocyte miR-27a Causes Hypertension by Reducing Mas Receptor Expression and Function in the Artery

X. Zou,[1] J. Wang,[1] C. Chen,[1] P.A. Jose,[2] C. Zeng,[1] [1]Cardiology, The Third Military Medical University, Chongqing, China; [2]Medicine, The George Washington University, Washington, DC

Essential hypertension has increased plasma concentrations of extracellular vesicles (EVs). Whether or not EVs are involved into pathogenesis of hypertension remains to be confirmed. Our present study found that injection of EVs from THP-1 cells, a monocyte cell line, to Sprague-Dawley (SD) rats increased blood pressure, accompanied by impaired Ang 1-7-mediated vasodilation in the mesenteric artery preconstricted with norepinephrine. In SD rats treated with EVs, Mas and phosphorylated eNOS expressions were decreased in the mesenteric artery. EVs from lipopolysaccharide (LPS)-incubated THP-1 cells further increased the blood pressure and impaired the Ang 1-7-mediated vasodilation. After the degradation of RNAs by RNase in EVs, the hypertensive effect of EVs disappeared, indicating the importance of RNAs in EVs in the hypertensive effect. Screening studies found miR-27a as a possible candidate, whose target gene is Mas, predicted by Target Scan and MiRTarBase softwares. Through loss- and gain-of function approaches, we found that miR-27a decreased Mas and phosphorylated eNOS expressions in human umbilical vein endothelial cells. The miR-27a in EVs is of physiological significance because injection of EVs from miR-27 transfected-HEK293 cells increased blood pressure in SD rats associated with impaired Ang 1-7-mediated vasodilation. Moreover, the expressions of Mas and phosphorylated eNOS were decreased in EV-treated rats. The above-mentioned phenomenon was reversed after down-regulation of miR-27a in EVs. Therefore, we conclude that monocyte miR-27a in EVs decreases Mas receptor expression in the endothelium and impairs endothelial NO release and Ang 1-7-mediated vasodilation, which are involved in the pathogenesis of hypertension.

Keywords: Extracellular vesicles, hypertension, Mas, endothelial cells

ARTERIAL STRUCTURE AND COMPLIANCE

LB-P-08

Role of GRK4 in the Regulation of Arterial AT1 Receptor in Hypertension

K. Chen,[1] C. Fu,[1] C. Chen,[1] P.A. Jose,[2] C. Zeng,[1] [1]Cardiology, The Third Military Medical University, Chongqing, China; [2]Medicine, The George Washington University, Washington, DC

G protein-coupled receptor kinase 4 (GRK4) gene variants, via impairment of renal dopamine receptor and enhancement of renin-angiotensin system functions, cause sodium retention and increase blood pressure. Whether or not GRK4 and the angiotensin type 1 receptor (AT1R) interact in the aorta is not known. We, now, report that GRK4 is expressed in vascular smooth muscle cells (VSMCs) of the aorta. Heterologous expression of the GRK4γ variant 142V in A10 cells increased AT1R protein expression and AT1R-mediated increase in intracellular calcium concentration. The increase in AT1R expression was related to an increase in AT1R mRNA expression via the NF-κB pathway. As compared with control, A10 cells expressing GRK4γ 142V had greater NF-κB activity with more NF-κB bound to the AT1R promoter. The increased AT1R expression in cells expressing GRK4γ 142V was also associated with decreased AT1R degradation, which may be ascribed to lower AT1R phosphorylation. There was a direct linkage between GRK4γ wild-type (WT) and AT1R that was decreased by GRK4γ 142V. The regulation of AT1R expression by GRK4γ 142V in A10 cells was confirmed in GRK4γ 142V transgenic mice; AT1R expression was higher in the aorta of GRK4γ 142V transgenic mice than control GRK4γ WT mice. Angiotensin II-mediated vasoconstriction of the aorta was also greater in GRK4γ 142V than WT transgenic mice. This study provides a mechanism by which GRK4, via regulation of arterial AT1R expression and function, participates in the pathogenesis of conduit vessel abnormalities in hypertension.

Keywords: hypertension, G protein coupled receptor kinase 4, angiotensin type 1 receptor, vasoconstriction

ANTIHYPERTENSIVE DRUGS AND PHARMACOLOGY

LB-P-09

Plasma Enalapril Kinetics of Two Modified Formulations Tested in Healthy Volunteers. A Pilot Trial Searching for an Optimum Blood Pressure Control

C. Incardona,[1] P. Lombardo,[1] E.C. Feleder,[2] G.A. Yerino,[2] E.K. Halabe,[2] J. Milei,[3] G. Ottaviano,[3] A. Muller,[3] E.J. Roldán.[1] [1]Medical Direction, Gador S.A., Buenos Aires, Argentina; [2]Clinical Research Unit, F.P. Clinical Pharma, Buenos Aires, Argentina; [3]Institute of Cardiological Research Prof. Dr. Alberto C. Taquini, Buenos Aires, Argentina

Enalapril maleate daily schedules are considered the most cost/efficient chronic therapy for blood hypertension in many countries. Notwithstanding in practice, some patients demand an extra dose before-night, in order to cover eventual nocturnal hypertension peaks, which in turn are related to increased morbidity and mortality. Enalapril blood levels can be modified in order to provide more active substance during the final hours of the day. Accordingly two different modified release (MR-1 and MR-2) formulations were developed at our R&D facilities (Gador SA, Buenos Aires) and clinically tested. In a GCP/ICH pilot study, enalapril plasma levels of MR-1 and MR-2, single 10 and 20mg doses, were assessed by liquid chromatography MS/MS in healthy volunteers (n=6). A purchased 20mg enalapril (Renitec, Merck & Co) served as a control. After signing consent, participants were randomly and cross-over treated with the study forms during 5 consecutive periods (single-dose), and subjected to repetitive blood samples during 24 hours at FP Clinical Unit. After completing all the period's results were clustered by formulation type and dose, showing MR-1/10mg mean (SD) variables were C_{max} =15.6±6.7ng/mL; T_{max}=1.2±0.5h; and $AUC_{0\text{-}inf}$=45.9±16.0ng.h/mL; MR-1/20mg C_{max} =61.3±85.9 ng/mL, T_{max}=1.1h and $AUC_{0\text{-}inf}$ =118.8±127.4 ng.h/mL; MR-2/10mg variables