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ORIGINAL ARTICLE

Endocan, a novel marker of endothelial dysfunction in patients with essential hypertension: Comparative effects of amlodipine and valsartan

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Abstract

Vascular inflammation plays an important role in the pathophysiology of hypertension and high levels of endocan may reflect ongoing vascular inflammation in hypertensive patients. In the present hypothesis-generating study, we aimed at investigating the comparative effects of amlodipine and valsartan on endocan levels in newly diagnosed hypertensive patients. The study population consisted of 37 untreated hypertensive patients who were randomized to the two treatment arms. After baseline assessment, each patient was randomly allocated to either 10 mg daily of amlodipine ($n = 18$, 7 males) or 160 mg daily of valsartan ($n = 19$, 3 males) and treated for a 3-month period. Sphygmomanometric blood pressure (BP) and serum endocan were measured before and every 2 weeks during drug treatment. There was no statistically significant difference between the two treatment arms as far as baseline socio-demographic and clinical characteristics are concerned. After a 3-month treatment period, systolic and diastolic BP values significantly reduced by antihypertensive treatment ($p < 0.001$). Furthermore, endocan levels were significantly decreased in both treatment arms ($p < 0.05$). However, amlodipine caused a greater percent decrease in circulating endocan levels compared with valsartan at the end of the treatment period. Both drugs reduced high sensitivity C-reactive protein values. However, the statistical significant difference vs baseline was achieved only in the group treated with amlodipine. No correlation was found between endocan plasma levels and BP reduction. The results of this hypothesis-generating study suggest that amlodipine and valsartan decrease endocan levels in newly diagnosed hypertensive patients. The effects, which are more evident with amlodipine, may contribute to the anti-inflammatory effects exerted by the two drugs on the vascular target.

Key Words: *Amlodipine, endocan, endothelium, valsartan, vascular inflammation.*

Introduction

Vascular endothelium plays a pivotal role in the regulation of cardiovascular homeostasis by producing and releasing different vasoactive substances, such as nitric oxide, endothelin and prostaglandins (1–3), which guarantee a physiological level of blood viscosity as well as the inhibition of the vascular inflammatory response and smooth muscle cell proliferation. In presence of cardiovascular risk factors and oxidative stress, however, the normal endothelial function is impaired with an imbalance in the endothelium-derived relaxing and contracting

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factors, increased vascular permeability, platelet aggregation, leukocyte adhesion/infiltration and generation of different cytokines, such as high sensitive C-reactive protein (hsCRP), E-selectin, P-selectine, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1) (4–8). Throughout these biological changes, endothelial dysfunction play an important role in the atherogenic process, increasing the risk of cardiovascular events (3,9–11).

Endocan, previously defined endothelial cell specific molecule-1 (ESM-1), is released by the endothelial cells (12) and represents a key modulator of major cellular processes, such as cells proliferation, leucocyte, ICAM-1, VCAM-1 adhesion and migration (13,14). In addition, endocan is altered in many endothelium-dependent pathological states, such as inflammation, cancer, infections, Behçet disease and psoriasis vulgaris (15–20), all conditions characterized by an endothelial dysfunction. This may explain why this substance is regarded as a novel marker of endothelial dysfunction. However, at best of our knowledge, only two studies (21,22) so far assessed plasma levels of endocan in newly diagnosed untreated hypertensive patients, showing a significant increase compared with controls (21). In one of these studies, endocan blood levels were also assessed during antihypertensive drug treatment, showing a tendency to their reduction during administration of an angiotensin II receptor blocker (22). Among anthypertensive agents, the inhibitors of the renin–angiotensin–aldosterone system and the dihydropiridine calcium channel blockers display some pleiotropic effects, because, independently of their blood pressure-lowering properties, these agents may improve endothelial dysfunction and decrease the levels of inflammatory and oxidative stress vascular markers (22–27). In the present hypothesis-generating study, we investigated the comparative effects of amlodipine and valsartan on endocan and C-reactive protein (CRP) levels in patients with newly diagnosed hypertension.

Methods

Study population

Forty-seven newly diagnosed hypertensive patients with a grade 1 hypertension according to the European Society of Hypertension–European Society of Cardiology 2013 guidelines (28) were originally enrolled in this single blind, randomized, prospective study. Of them, 10 patients were withdrawn from the study for several reasons, i.e. five patients (three in the amlodipine group and two in valsartan group) for lack of compliance at the third month of therapy, five other patients because they were non-responders to either amlodipine (two patients) or valsartan (three patients). Participants were recruited among 176 hypertensive patients with different risk factors, admitted to cardiology and internal medicine outpatient clinics. The study was carried out in accordance with the Declaration of Helsinki and all patients gave their informed consent. Patients with secondary hypertension, inflammatory diseases, asthma or chronic obstructive lung disease, atrial fibrillation or recurrent tachyarrhythmias, anemia, diabetes mellitus, insulin resistance, impaired glucose tolerance, body mass index ≥ 27 kg/m^2, heart failure, valvular disease, cerebrovascular accident within the last 6 months, history of coronary artery disease or proven coronary artery disease, any abnormality in thyroid function tests, renal or hepatic dysfunction (creatinine >1.5 mg/dl, aspartate aminotransferase and alanine transaminase more than twice the upper limit of normal, respectively), pregnancy or nursing and patients treated with medication that could affect blood pressure or interfere with measurement of endocan and CRP were excluded from the study. No patient was under calcium and/or vitamin D supplementation.

After baseline clinical assessment, patients were randomly assigned to 10 mg daily of amlodipine (group I, $n=18$, seven males) or 160 mg daily of valsartan (group II, $n=19$, three males) and treated for 3 months. Randomization was done using a table of random numbers. Blood pressure, heart rate, treatment compliance and tolerability were evaluated every 2 weeks. Laboratory analyses were performed by an investigator unaware of the assigned drugs, at baseline and at the end of treatment. If systolic and diastolic blood pressure, measured at the end of the second week of the treatment, were not normalized (<140 mmHg and <90 mmHg, respectively), patients were regarded as non-responders and withheld from the study (see above). All patients followed the National Cholesterol Education Program step I cholesterol lowering and salt-restricted diet during the treatment period (29).

Measurements

Blood pressure measurement. Blood pressure was measured by the same investigator, unaware of the experimental design of the study, three times on the right arm in the sitting position, following 20 min resting, using a mercury sphygmomanometer. The average of the three measurements was used for the analysis. Phase I and V Korotkoff sounds were employed to assess systolic and diastolic blood pressure, respectively. Hypertension was diagnosed when the systolic BP was ≥ 140 mmHg and the diastolic BP was ≥ 90 mmHg.

Blood chemistry. Blood samples were drawn from an antecubital vein by venipuncture, avoiding stasis at 07–08:00 h, after 20 min of supine rest, following fasting for ≥ 12 h. Total plasma

cholesterol, triglyceride and high-density lipoprotein-cholesterol (HDL-C) were measured by an enzymatic colorimetric method using an Olympus AU 600 autoanalyser and reagents from Olympus Diagnostics GmbH (Hamburg, Germany). Low-density lipoprotein-cholesterol (LDL-C) levels were calculated by the Friedewald formula (30). Blood glucose was measured by the glucose oxidase method. Serum hsCRP was determined by an ELISA method (Oxis ELISA kit; Oxis, Portland, OR).

Endocan blood levels assay. Human endothelial-cell endocan (ESM-1) was assayed by an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol (Hangzhou Eastbiofarm Co. Ltd., Hangzhou, China). Intra-assay coefficient of variation of endocan assay was $< 10\%$ while inter-assay coefficient of variation was $< 12\%$. The minimum detectable concentration for endocan was 2.56 ng/l. Measurements were carried out using microtiter plate reader Bio-Tek Synergy HT (Biotek Instruments Inc., Winooski, VT, USA). All samples were evaluated in duplicate. Linear measurement range of the assay was 5–1500 ng/l.

Statistical analysis

Statistical analyses were performed by using SPSS 15.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were given as median (interquartile range, 25–75%) and categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov–Smirnov test. The statistical differences between groups were tested for significance by chi-square and Mann–Whitney U tests. Wilcoxon test was used to compare continuous variables before and after drug therapy. Correlation between variables was carried out using the Spearman correlation test. Differences were considered significant at $p < 0.05$ two-sided.

Results

Thirty-seven patients completed the study, 18 in the amlodipine (median age: 46 years, seven males) and 19 in the valsartan (median age: 47 years, three males)-treated group. As shown in Table I, at baseline the two groups of patients were homogeneous regarding demographic, clinical characteristics, biochemical parameters, endocan and hsCPR concentrations (187 vs 196 ng/l, $p = 0.83$ and 3.97 vs 4.19 mg/l, $p = 0.89$) respectively. After 3 months of treatment, systolic, diastolic BP and mean blood pressure significantly decreased with amlodipine and with valsartan ($p < 0.001$ vs baseline), without significant difference between the two drugs (Figure 1).

Figure 2 shows the effects of amlodipine and valsartan treatment on the biochemical markers of endothelial function (upper panels) and inflammation (lower panels) assessed in the present study. Endocan plasma concentrations were significantly reduced by amlodipine from 187 to 115 ng/l (-72 ng/l, $p = 0.006$) and by valsartan from 196 to 164 ng/l (-32 ng/l, $p = 0.022$), compared with the pre-drug control values (Figure 2, upper panel), without evidence of any difference in the statistical significance between the two drugs. However, at end of treatment, the percent reduction of plasma endocan levels tended to be more pronounced in patients under amlodipine treatment (-38.5%) than in those

Table I. Baseline demographic, clinical and laboratory data of the study patients.

	Amlodipine ($n = 18$)	Valsartan ($n = 19$)	p
Age (years)	46 (42–56)	47 (38–51)	< 0.510
Gender (M), n (%)	7 (39)	3 (16)	< 0.151
BMI (kg/m^2)	30 (28–32)	29 (26–34)	< 0.855
Smoking, n (%)	3 (17)	6 (32)	< 0.226
Alcohol use, n (%)	1 (5.5)	0 (0)	< 1.000
Dyslipidemia, n (%)	0 (0)	1 (5.3)	< 1.000
Aspirin use, n (%)	0 (0)	1 (5.3)	< 1.000
Statin use, n (%)	0 (0)	1 (5.3)	< 1.000
Glucose (mg/dl)	95 (90–104)	94 (89–102)	< 0.595
Urea (mg/dl)	26 (21–31)	30 (22–34)	< 0.229
Creatinine (mg/dl)	0.87 (0.78–0.94)	0.85 (0.78–0.91)	< 0.503
Total cholesterol (mg/dl)	210 (195–241)	230 (201–255)	< 0.334
Triglyceride (mg/dl)	135 (101–188)	122 (97–172)	< 0.605
Hemoglobin (g/dl)	14.5 (14–16)	14.3 (14–15)	< 0.594
WBC ($\times 10^9$/l)	6.95 (5.47–7.77)	6.90 (6.30–8.30)	< 0.475
Platelets count ($\times 10^9$/l)	249 (207–266)	263 (229–302)	< 0.171
Endocan (ng/l)	185 (134–463)	193 (129–376)	< 0.540

Values are shown as medians (25–75%) or percent numbers (%). BMI, body mass index; WBC, white blood cell.

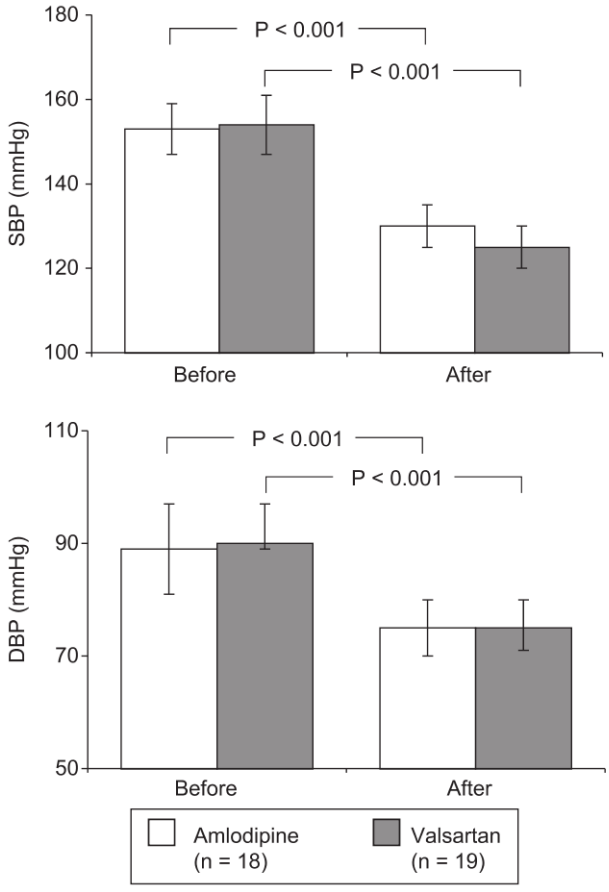

Figure 1. Effects of a 3-month treatment with amlodipine or valsartan on sphygmomanometric systolic (S, upper panel) and diastolic (D, lower panel) blood pressure values. Data are shown as medians (25–75%).

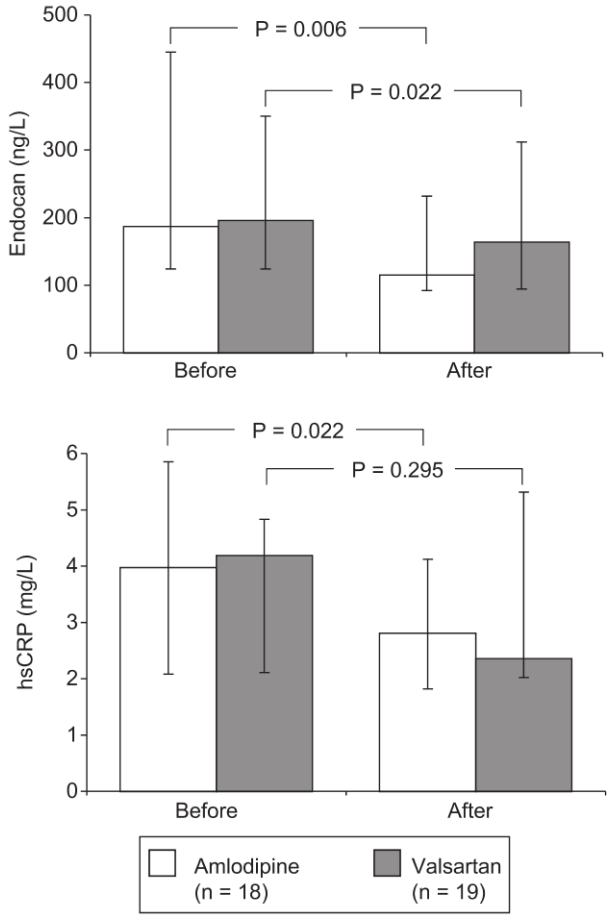

Figure 2. Effects of a 3-month treatment with amlodipine or valsartan on endocan circulating plasma levels (upper panel) and C-reactive protein (CRP, lower panel). Data are shown as medians (25–75%).

treated with valsartan (−16.3%). Levels of CRP were reduced by both drugs, but the reduction achieved statistical significance ($p = 0.022$) in the amlodipine-treated group only (Figure 2, lower panel). The results obtained were similar in the menopausal and in non-menopausal female patients. On correlation analysis, no statistically significant relationship was found between percent changes in endocan, blood pressure and CPR induced by antihypertensive drug treatment in the whole study population (Table II).

Discussion

The present hypothesis-generating study provides a series of new data on the behavior of circulating plasma levels of endocan in newly diagnosed hypertensive patients and on the effects of amlodipine or valsartan treatment. First, endocan plasma concentrations in our patients were higher than those detected in healthy normotensive subjects (20) and almost superimposable on the ones reported in another study (21). Second, the elevated circulating plasma levels of endocan and CRP values we found in our grade I essential hypertensive patients suggest that the blood pressure elevation was already associated with an endothelial dysfunction and/or endothelial activation. Third, after 3 months of treatment, both amlodipine and valsartan significantly decreased the endocan plasma concentrations, the reduction being almost superimposable in the two treatment groups. Our data also suggest, however, that amlodipine was more effective than valsartan in this regard, because the percent reduction in endocan we observed in the patients treated with the calcium channel blocker was greater for magnitude than the one detected in the angiotensin II receptor blocker-treated patients. Fourth, the reduction in endocan and CRP values suggests that both drugs induced an

Table II. Correlations between percent change of endocan levels and corresponding blood pressure and C-reactive protein percent changes induced by treatment in the whole population sample of the study.

Variable	r*	p
SBP, percent change	−0.090	0.598
DBP, percent change	0.195	0.247
CRP, percent change	−0.055	0.749

SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein. *Spearman correlation analysis.

improvement in endothelial dysfunction in our subjects. Fifth, the reduction in CRP values achieved statistical significance only in the amlodipine-treated group, suggesting that the calcium channel blocker was more effective in inhibiting this inflammatory marker in our patients.

Other results of the present study deserve to be briefly mentioned. First, in our patients no significant relationship was found between the percent change in endocan or CRP plasma levels and BP, suggesting that the effects of amlodipine and valsartan might be independent on the BP reduction. This finding is in agreement with the results of another study (21), in subjects with hypertension treated with amlodipine, but disagree with the positive correlation between serum endocan and plasma CRP observed in untreated newly diagnosed hypertensive patients in another study (20). Second, in our patients we found that when expressed as percent figures the endocan reduction was greater for magnitude in the amlodipine-treated than in the valsartan-treated group. Although our study does not allow us to explain this difference we can speculate that the greater pleiotropic effects of amlodipine compared with valsartan on endothelial dysfunction might be involved.

Our study has some limitations but also a clinical implication. The first limitation refers to the small sample size of the study population, which may restrict our conclusions to stage 1 hypertensive patients we examined in the present study. The second limitation refers to the lack of a control no-treatment group, which would have allowed the study conclusions to be strengthened, also allowing us to exclude that the results should depend, at least in part, on a regression to the mean phenomenon. The third and final limitation refers to the fact that ethical reasons did not allow us to perform a direct assessment of the endothelial function via invasive methods in the no-drug condition and to repeat it following a 3-month period. However, evidence exists that endocan levels may be regarded an acceptable surrogate marker of endothelial function (12,15–19) to be used in specific observational and/or intervention studies. Evidence also exists (31,32) that assessment of the effects of amlodipine or valsartan on endothelial function by invasive methods may provide similar results. The clinical implication refers to the evidence provided by our data that the favorable effects of amlodipine and valsartan treatment in reducing endocan levels and in improving vascular inflammation may be an important feature of the cardioprotective properties of these drug, participating at their favorable impact on the cardiovascular risk profile of the hypertensive patients. Further data, however, are needed to confirm the results of this hypothesis-generated investigation in a large-scale controlled clinical study.

Declaration of interest: No conflict of interest declared.

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