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The effect of one-month amlodipine treatment on plasma endothelin-1 concentration in hypertensive patients

Wpływ jednomiesięcznego podawania amlodipiny na osoczowe stężenie endoteliny-1 (ET-1) u pacjentów z nadciśnieniem tętniczym

Streszczenie

Wstęp Ochrona śródbłonka naczyniowego i mięśni gładkich naczyń w następstwie zastosowania antagonistów wapnia jest związana z wieloma mechanizmami, spośród których oddziaływanie na endotelinę-1 (najsilniej działającą kurcząco na naczynia substancję endogenną) wydaje się niesłychanie istotne. Celem pracy była ocena wpływu amlodipiny (antagonisty wapnia, pochodnej dihydropirydyny III generacji) na osoczowe stężenie endoteliny-1 (ET-1) oraz stężenie aldosteronu (Ald) w surowicy chorych z pierwotnym nadciśnieniem tętniczym (EH).

Materiał i metody Grupa badana liczyła 39 pacjentów (18 kobiet i 21 mężczyzn) z EH w stadium I wg klasyfikacji WHO. Do badań nie zakwalifikowano chorych z wtórnymi postaciami nadciśnienia tętniczego oraz chorobami mogącymi wpływać na stężenie ET-1.
U wszystkich badanych oceniano następujące parametry:
— SBP — ciśnienie tętnicze skurczowe;
— DBP — ciśnienie tętnicze rozkurczowe;
— ET-1 — stężenie ET-1 w osoczu;
— Ald — stężenie aldosteronu w surowicy;
przed (I badanie) i po 30 dniach podawania amlodipiny w dawce 5 mg/dobę (II badanie).

Wyniki Leczenie amlodipiną przez 30 dni (5 mg/d.) spowodowało:
1. Istotne obniżenie SBP (średnia ± SD: I badanie: 160,17 ± 9,76 *v.* II badanie: 131,78 ± 11,83 mm Hg, p = 0,0000001).
2. Istotne obniżenie DBP (średnia ± SD: I badanie: 93,58 ± 7,71 *v.* II badanie: 74,17 ± 10,03 mm Hg, p = 0,0000001).
3. Nieistotne statystycznie obniżenie ET-1 (mediana ± S: I badanie: 83,3 ± 23,9 *v.* II badanie: 78,7 ± 20,85 pg/ml, p = 0,102).
4. Nieistotne statystycznie podwyższenie Ald (mediana ± S: I badanie: 125,9 ± 66,53 *v.* II badanie: 158,49 ± 76,15 pg/ml, p = 0,52).

Wnioski Terapia amlodipiną przez 30 dni w dawce 5 mg/dobę u pacjentów z EH prowadziła do nieistotnego statystycznie obniżenia stężenia ET-1, co może mieć znaczenie dla zastosowania tego leku w codziennej praktyce. Jednak ograniczeniem opisywanego badania była stosunkowo niewielka liczebność grupy badanej (39 chorych), co przemawia za potrzebą poszerzenia badań.

słowa kluczowe: endotelina-1, amlodipina, pierwotne nadciśnienie tętnicze, antagoniści wapnia
Nadciśnienie Tętnicze 2011, tom 15, nr 1, strony 5–12

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Introduction

Endothelial cells are located between circulating blood and vascular smooth muscle. Nowadays, these cells are regarded as an endocrine organ, rele-

asing numerous vasodilatative and vasoconstrictive substances. Although among them prostacyclin, bradykinin, nitric oxide and endothelium-derived hyperpolarizing factors play a vasodilatative role, angiotensin II and endothelin-1 are the most important vasoconstrictors. Moreover, the last mentioned also exerts mitogenic, prothrombotic and inflammatory action.

Calcium antagonists (Ca-A), especially 1.4-dihydropiridine, have been widely used for the treatment of many cardiological disorders, not only because of their haemodynamic and electrophysiological properties, but also because of those concerning vascular protection. These last effects are especially important in the face of the dysfunction of the endothelium, commonly observed in most internal disorders, cardiovascular, in particular.

Endothelium and smooth muscle protection after Ca-A are markedly related to several mechanisms, among which the most important are:

1. Vasorelaxation modulated by the improvement of endothelial nitric oxide (NO) availability. This effect may be partially associated with the decrease of angiotensin II, since this substance stimulates NAD(P)H oxidase-responsible for the formation of superoxide, which inactivates NO. Also kinins (what has been proved in another model with amlodipine treatment) may release NO from microvessels [1].

2. Calcium antagonist activity. In fact, this mechanism is very unlikely since endothelial cells do not express voltage-operated calcium channels. On the other hand, however, it should be recognized, that these drugs counteract angiotensin II and ET-1 at the level of vascular smooth muscle by reducing the inflow of calcium ions (Ca^{2+}) [2].

3. Antioxidant effects and protection against free radical injury. It has been noted that nifedipine decreases circulating parameters of oxidative stress and prevents the effect of the antioxidant vitamin C [3, 4]. Moreover, amlodipine has preserved plasma total superoxide dismutase (SOD) activity in animal models [5]. However, even the strongest up-regulation of SOD activity was observed after treatment with pranidipine [6].

4. Anti-atherogenic reaction. This property has been described in many experimental and clinical studies, and, what is very interesting, has been observed independently of blood pressure reduction or plasma lipids changes [7].

5. Probably anti-endothelin activity. Endothelin-1 (ET-1) is a 21-amino-acid peptide synthesized and released primarily in the vascular endothelium, and is regarded as the most powerful endogenous vasoconstrictor. Since its first description [8] it has been the subject of intense research which has revealed also mitogenic property of ET-1. Many physical and chemical stimulatory factors of ET-1 synthesis have been described, among them: increase of shear stress, adrenaline, angiotensin II, vasopressin, transforming growth factor β, interleukin-1 (IL-1), IL-2, IL-3, thrombin and insulin. Some substances may inhibit ET-1 production: nitric oxide, bradykinin, cGMP, prostacyclin, natriuretic peptides and heparin [9].

Moreover, the role of ET-1 in the pathogenesis of a variety of cardiovascular and non-cardiovascular diseases has been established. This peptide has been especially recognized as an important element in the pathogenesis of arterial hypertension. Since then, the influence of various types of antihypertensive drugs on ET-1 synthesis and effects have been assessed in many experimental and clinical studies.

Mechanisms involved in the interaction between Ca-A and ET-1 have been also described. They include:

Interaction through voltage-operated Ca^{2+} channels

It has been observed that ET receptors on the vascular smooth muscle in the coronary artery are linked to voltage-operated Ca^{2+} channels via G proteins [10].

ET(A) receptor couples to Gq/11 protein leading to transduction of receptor signals, playing also a role in Ca^{2+} mobilization. Despite the evidence observed in many studies that ET-1 receptor stimulation via the above-mentioned Gq/11 protein induces an increase in intracellular Ca^{2+}, this has not been proved by all researchers [11].

Influence of sarcoplasmatic-endoplasmatic reticulum Ca^{2+}-ATPase on the ability of an ET receptor antagonist to inhibit the ET-1 constriction was assessed by Tosun *et al.* [12]. This study indicated that lowered sarcoplasmatic-endoplasmatic reticulum Ca^{2+}-ATPase activity decreases the ability of an ET receptor antagonist to inhibit the ET-A receptor, which may be related to the opening of store-operated channels leading to the enhancement of the internalization of the ET-A receptor.

Phospholipase C and diacylglycerol

Activation of ET receptors releases the cascade of phospholipase C and diacylglycerol with increased formation of inositol triphosphate, which releases Ca^{2+} from the sarcoplasmatic reticulum leading to increased cytosolic Ca^{2+} [13].

Ca^{2+}-activated K^+ channels

Activation of Ca^{2+}-activated K^+ channels with the high degree of conductance by ET-1 provoked a capacitative Ca^{2+} influx which induced endothelial cell proliferation [14].

Inhibition of sympathetic system

Despite the widely-described activation of the sympathetic nervous system observed after short-acting dihydropyridines, adverse effects have been also presented in some studies. Vasoconstriction caused by phenylephrine [15, 16] or other α-agonist [17] was reduced by nifedipine [18], diltiazem [15], amlodipine [16], verapamil [17] and nitrendipine [17].

Influence on NO availability

The fact that NO is an inhibitor of ET-1 synthesis, and widely mentioned in many studies, may be partially responsible for interaction between Ca-A and ET-1.

As has already been described nifedipine increased NO bioavailability in essential hypertension, probably partially due to the antioxidant efficacy of this drug [3, 4]. Therefore, the vasodilatative effect observed, especially after dihydropyridines, is inhibited in the presence of NO-synthase inhibitors [19].

Objectives

The aim of this study was to investigate the influence of amlodipine (dihydropyridine calcium channel blocker, III generation) on plasma endothelin-1 (ET-1) and serum aldosterone (Ald) concentration in patients with essential arterial hypertension (EH).

Material and methods

The study population included 39 patients (18 women and 21 men) with EH in stage I according to WHO classification. Selection criteria excluded patients with a secondary form of arterial hypertension and any additional diseases influencing ET-1 plasma concentration, like diabetes mellitus, angina pectoris, autoimmune disorders and renal diseases with impairment of renal function. The mean systolic blood pressure (SBP) was 160.17 ± 9.76, the mean diastolic blood pressure (DBP) was 93.58 ± 7.71. In the fundoscopic findings, grade I was observed in 7 patients, s grade I/II — in 16 ones and grade II in 16 individuals. The average age of the study population was 59.89 ± 9.13 years.

Clinical and biochemical characteristics of hypertensive patients included in the study before the treatment with amlodipine (tab. I).

In all of the patients the following parameters were assessed:

— SBP — systolic blood pressure;

— DBP — diastolic blood pressure;

Table I. Evaluated parameters

Tabela I. Charakterystyka badanych

Gender (F/M)	18/21
Age (years)	59.89 ± 9.13
SBP [mm Hg]	160.17 ± 9.76
DBP[mm Hg]	93.58 ± 7.71
Glucose [mmol/l]	5.08 ± 0.49
Creatinine [mmol/l]	79.41 ± 14.43
Urea [mmol/l]	5.81 ± 1.33
K^+ [mmol/l]	4.46 ± 0.27
Total cholesterol [mmol/l]	5.15 ± 1.21
LDL [mmol/l]	3.01 ± 1.02
ET-1 (plasma) [pg/ml]	83.3 ± 23.9
Ald (serum) [pg/ml]	125.9 ± 66.53

SBP — systolic blood pressure, DBP — diastolic blood pressure, K+ — serum potassium concentration, LDL — serum low-density lipoprotein concentration, ET-1 — plasma endothelin-1 concentration, Ald — serum aldosterone concentration
Data are presented as mean ± SD, except ET-1, aldosterone concentration presented as median ± S

— ET-1 — endothelin-1 plasma concentration;

— Ald — aldosterone serum concentration;

before (I study) and after 30-day treatment with amlodipine in dose 5 mg/day (II study).

Patients were asked to fast overnight (from food, caffeine, tobacco, alcohol and drugs). In the majority of cases the patients did not undergo anti-hypertensive treatment before investigation, while in some situations amlodipine was added to the treatment which did not influence ET-1 concentration. Blood samples were collected during rest (lasting for at least 2 hours), in a lying position.

Blood samples for the determination of plasma ET-1 were drawn into prechilled EDTA tubes on ice, centrifuged at 2500 g for 10 min. The plasma was frozen at –70°C and stored for 2–7 weeks. Plasma levels of ET-1 and serum Ald concentration were estimated with radioimmunoassay (ET-1: DRG International Inc., USA; Ald: Immunotech SA, France).

Statistical analysis

Wilcoxon's test was used to check the statistical significance of the difference between nonparametric values. Correlations between parameters were assessed by using Spearman's tests. Results were expressed as mean ± SD, apart from ET-1 and Ald which were expressed as median ±S. Differences were considered statistically significant at a value of $p < 0.05$.

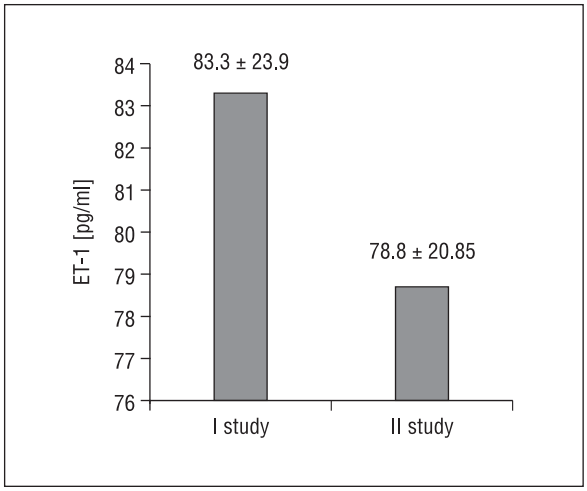

Figure 1. ET-1 plasma conc. in EH patients before (I study) and after (II study) 30-day therapy with amlodipine 5 mg/day

Rycina 1. Stężenie ET-1 w osoczu pacjentów z EH przed (I badanie) i po (II badanie) 30-dniowej terapii 5 mg amlodipiny na dobę

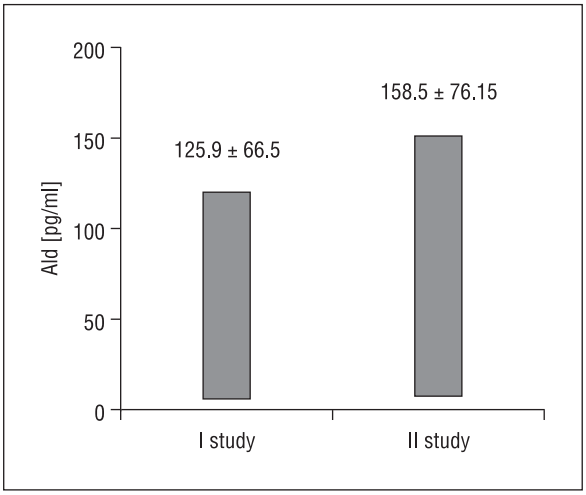

Figure 2. Ald conc. in EH patients before (I study) and after (II study) 30-day therapy with amlodipine 5 mg/day

Rycina 2. Stężenie Ald w surowicy pacjentów z EH przed (I badanie) i po (II badanie) 30-dniowej terapii 5 mg amlodipiny na dobę

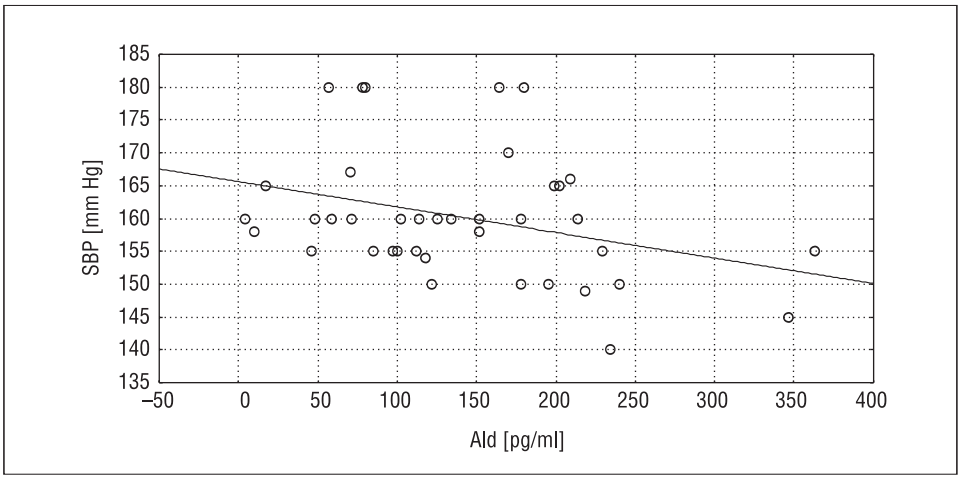

Figure 3. Correlation between Ald conc. (before treatment) and SBP (before treatment), p = 0.042

Rycina 3. Korelacja między stężeniem Ald (przed leczeniem) a SBP (przed leczeniem), p = 0,042

Results

30-day treatment with amlodipine (5 mg/day) led to:

— a significant decrease of SBP (Mean ± SD: I study: 160.17 ± 9.76 vs II study: 131.78 ± 11.83 mm Hg, p = 0.0000001);

— a significant decrease of DBP (Mean ± SD: I study: 93.58 ± 7.71 vs II study: 74.17 ± 10.03 mm Hg, p = 0.0000001);

— a non-significant decrease of ET-1 conc. (Median ± S I study: 83.3 ± 23.9 vs II study: 78.7 ± 20.85 pg/ml, p = 0.102) (fig. 1);

— a non-significant increase of Ald conc. (Median ± S I study: 125.9 ± 66.53 vs II study: 158.49 ± 76.15 pg/ml, p = 0.52) (fig. 2).

We also observed a correlation between Ald conc. (before treatment) and SBP (before treatment), p = 0.042 (fig. 3) and a correlation between changes in ET-1 conc. and changes in DBP, p = 0.026 (fig. 4).

Discussion

The influence of calcium antagonists on endothelin-1 (ET-1) concentration have been assessed in several studies. In some research, a decreased, unchanged, or even increased ET-1 concentrations after Ca-A therapy have been noted.

In a very interesting study by Krenek *et al.* [20] the effect of long-term treatment with lacidipine in salt-

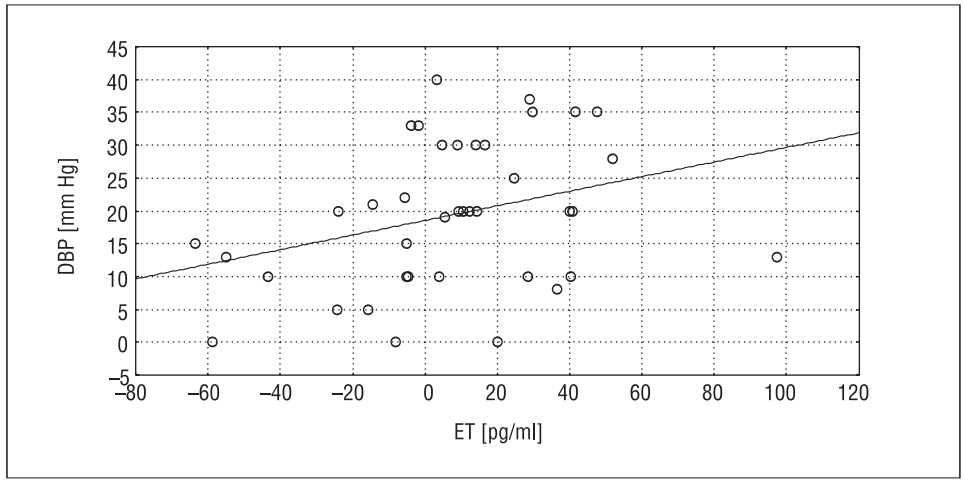

Figure 4. Correlation between changes of ET-1 conc. and changes of DBP, p = 0.026
Rycina 4. Korelacja między zmianami stężenia ET-1 a zmianami DBP, p = 0,026

loaded stroke-prone hypertensive rats on endothelium dependent vasorelaxation was assessed. High-sodium diet (1% NaCl in drinking water) induced elevated blood pressure and aortic weight, wall thickness, and increased plasma renin activity PRA (from 5.3 ± 0.8 to 13.0 ± 2.8 ng/ml/h) whereas the parameters of endothelium dependent vasodilatation was significantly decreased. Also preproendothelin-1 levels were elevated twofold ($p < 0.01$). Six weeks of treatment with lacidipine at a dose of 1 mg/kg/day prevented these structural and functional aortal abnormalities, among which the increase of preproendothelin-1 mRNA was also completely prevented. The explanations for this were various. The antioxidant efficacy of calcium antagonists, with secondarily increased bioavailability of NO was taken into account as a possible reason. Decreased PRA after lacidipine, with a secondary decrease of angiotensin II production might also have contributed to the prevention of preproendothelin-1 over-expression.

Moreover, in a study by Godfraind *et al.* [21] lacidipine administered in spontaneous hypertensive stroke-prone rats reduced endothelin production previously enhanced by a high-salt diet.

Yang *et al.* reported that pranidipine suppressed basal and thrombin-stimulated ET-1 production in endothelial cells. This drug also enhanced the vasodilatatory effect of NO, by releasing NO from endothelial cells and by increasing of cGMP accumulation in vascular smooth muscle cells [6].

Positive effects have also been noted after five weeks of administering benidipine in subdepressor doses — 1 mg/kg/day in salt-sensitive hypertensive rats, and resulted in a significant improvement of myocardial remodeling and left ventricular hypertrophy. These beneficial effects might be partially associated with decreased ET-1 expression in the left ventricle observed after benidipine treatment [22].

On the other hand, Hishikawa *et al.* reported significant increase of ET-1 release from cultured human umbilical vein endothelial cells provoked by pressure, but this process was not affected by nifedipine administration (5 μmol/l) [23].

In a study by Åsberg *et al.*, the effects of long-term treatment with slow-release nifedipine (30–60 mg s.i.d.) or lisinopril (10–20 mg s.i.d.) on microvascular function in hypertensive renal transplant recipients were assessed. In fact, more beneficial effects were observed after lisinopril than after nifedipine treatment. Whereas in the nifedipine group plasma ET-1 concentrations were 0.44 ± 0.19 fmol/ml, in the lisinopril group they were significantly lower, and reached values 0.34 ± 0.10 fmol/ml, p = 0.048. Moreover, in controls ET-1 concentrations were 0.29 ± 0.09 fmol/ml. Such results may indicate a endothelial protective effect of lisinopril only. According to these authors, the higher plasma ET-1 level observed in the calcium antagonist group may be associated with decreased NO activity (inhibitor of ET-1 synthesis), as a result of endothelial dysfunction *per se*, or decreased NO bioavailability caused by higher angiotensin II concentration in the Ca-A group than in patients treated with an angiotensin-converting enzyme inhibitor [24].

Many studies have revealed that dihydropyridine Ca-A, especially the administration of short-acting drugs, and in some observations even after the chronic administration of those which are long-acting, have led to the activation of the sympathetic nervous and renin-angiotensin systems [25, 26]. It has been also widely described that angiotensin II and norepinephrine may activate ET-1 synthesis and could pro-

voke over-expression of growth factors [8]. Such neurohormonal changes observed after Ca-A might limit their antihypertrophic effects. This theory has been proved in an experimental setting when high-dose amlodipine (20 mg/kg/day), previously reported to stimulate the renin-angiotensin and sympathetic nervous systems, provoked over-expression of preproendothelin-1 mRNA levels in the ventricles and aorta in Sprague-Dawley rats. This result was linked to higher relative left ventricular mass, observed after long-term administration (5 weeks), and higher relative right ventricular mass noted both after long- and short-term treatment (5 days) with amlodipine [27].

Regarding these data, we decided to assess the influence of amlodipine in such a dose (5 mg/day) that is not expected to influence neurohormonal balance. In fact, our results showed no effects on PRA and Ald concentrations after one month of amlodipine treatment, and as a consequence of these facts no influence of the renin-angiotensin-aldosteron system on ET-1 concentration should be mentioned.

It is also noteworthy, that as in previously described studies concerning the influence of Ca-A on ET-1 concentration, also the effect of amlodipine on ET-1 is unclear. Treatment with amlodipine may lead to an increase of ET-1 values, as in a study by Inigo *et al.* [28], where this drug, when administered to renal transplant recipients caused significantly higher ET-1 concentration compared with a group of patients undergoing losartan treatment. On the other hand, some studies have not revealed any influence of amlodipine on ET-1. Such results were observed for example in a study by Salomon *et al.* [29], where one month of treatment with amlodipine (5–10 mg/day) in patients with congestive heart failure (NYHA II and III) did not change plasma ET-1 concentration despite the improvement of circulatory efficiency assessed according to the NYHA classification. In the same way, Chen *et al.* [30] also demonstrated that amlodipine monotherapy in spontaneous hypertensive rats had no detectable effects on intrarenal endothelin concentration. These results are in agreement with findings of our research. Despite the fact that we observed a tendency toward decreased ET-1 concentration after 30-day treatment with 5 mg of amlodipine in hypertensive patients, this effect was not statistically significant. However, regarding the above-mentioned study by Inigo *et al.*, it is very important to notice that amlodipine did not increase ET-1 concentration in our group.

It should be also mentioned here, that in an experimental model of congestive heart failure provoked by doxorubicine in rats and mice, two weeks of amlodipine treatment (at a dose of 0.07 mg/day) reversed a large increase in endothelin-1 concentration [31].

There is also growing evidence that Ca-A may influence ET-1 effects both in humans and in animals. In a study by Kiowski *et al.* [32], a low-dose of ET-1 infusion (0.5 ng/min) in healthy, normotensive volunteers resulted in a significant increase in forearm blood flow, while high-doses of peptide (25 or 50 ng/min) led to vasoconstriction. Although treatment with Ca-A- nifedipine in doses of 0.25; 0.5 or 3 μg/min per 100 ml forearm tissue, resulted in a dose-dependent increase of forearm blood flow ($p < 0.05$), not only when nifedipine was administered alone, such results were also observed after co-infusion of both ET-1 and nifedipine. In comparison, such ceasing of ET-1 vasoconstrictor activity was also noted after verapamil administration in a dose of 80 μg/ /min per 100 ml forearm tissue. In conclusion, both verapamil (non-dihydropiridine Ca-A) and nifedipine (dihydropiridine Ca-A) prevented the ET-1 induced decrease in forearm blood flow.

In another study Rabelink *et al.*, the effects of ET-1 infusion on renal function in humans were assessed. A twofold increase in plasma ET-1 levels did not influence renal and systemic hemodynamics, while sodium excretion was significantly blunted. Whereas ET-1 infusion resulting in a threefold-increased peptide concentration in plasma significantly decreased renal plasma flow, the glomerular filtration rate, increased filtration fraction, renal vascular resistance, as well as sodium retention. Pretreatment with nifedipine at a dose which did not influence blood pressure (0.01 mg/kg/hr) attenuated renal vascular resistance and the antinatriuretic effects of ET-1 [33].

Moreover, a study by Kaasjager *et al.* [34] was designed to assess whether ET-induced renal vasoconstriction in humans may be stopped by nifedipine. The administration of the drug (priming dose 0.015 mg/kg, maintenance infusion 0.015 mg/kg/hr) on a top of ET-1 infusion reversed all the changes caused by ET-1, such as increased renal vascular resistance, sodium retention, decreased lithium clearance. No effect on the increased filtration fraction was observed, suggesting that influence of ET-1 and nifedipine on renal microcirculation did not overlap completely.

Recently the chronic effects of the nifedipine gastrointestinal therapeutic system (GITS) on vasoconstriction caused by ET-1 infusion in normotensive patients, and in those with essential hypertension, has been tested. ET-1 at a dose of 0.5 μg/100 ml of forearm tissue per minute caused a slight vasodilatation in normotensive but not in hypertensive pa-

tients. Higher doses of peptide (25; 50 μg/100 ml) led to dose-dependent vasoconstriction in both groups, and there were no differences between hypertensive normo- and hypercholesterolemic patients. Long-term treatment (24 weeks) with nifedipine GITS (30–60 mg/day) in hypertensive subjects diminished these consequences of ET-1 [18].

Ca-A may be also used during cyclosporine administration in transplant recipients. It has been recognized that renal dysfunction induced by cyclosporine A is associated with renal ET receptor up-regulation and increased urinary ET excretion. Moreover, treatment with nifedipine in rats during cyclosporine A administration had the ability to attenuate urinary ET excretion, without any influence on ET receptors [35].

The results of the above-presented research are especially interesting because of disagreement between the widely-described positive influence of Ca-A on ET-1 effects (the stopping of many changes caused by ET-1) and the poorly-documented effects of this group of drugs on ET-1 concentration (also observed in our study). It should be taken into consideration that the ET system is an autocrine/paracrine system and plasma concentration may reflect a "spill over" from local vascular production rather than true local activity.

Conclusion

In conclusion, 30-day treatment of essential hypertensive patients with amlodipine at a dose of 5 mg/day induced a non-significant decrease of ET-1 concentration which may be important for the therapeutic use of amlodipine in everyday practice. However, it should be also noted that our data were collected from a relatively small group of patients (39), and probably need to be confirmed in larger population sample.

Summary

Background Endothelium and smooth muscle protection after calcium antagonists (Ca-A) are markedly related to several mechanisms, among which the influence on endothelin-1 (a substance regarded as the most powerful endogenous vasoconstrictor) seem to be very important.

The aim of this study was to investigate the influence of amlodipine (dihydropyridine Ca-A, III generation) on plasma endothelin-1 (ET-1) and serum aldosterone (Ald) concentration in patients with essential arterial hypertension (EH).

Material and methods The study population included 39 patients (18 women and 21 men) with EH in stage I according to WHO classification. Selection criteria excluded patients with a secondary form of arterial hypertension and any additional diseases influencing ET-1 plasma concentration.

In all of the patients the following parameters were assessed:

— SBP — systolic blood pressure;

— DBP — diastolic blood pressure;

— ET-1 — endothelin-1 plasma concentration;

— Ald — aldosterone serum concentration;

before (I study) and after 30-day treatment with amlodipine in dose 5 mg/day (II study).

Results 30-day treatment with amlodipine (5 mg/day) led to:

1. Significant decrease of SBP (Mean ± SD: I study: 160.17 ± 9.76 vs II study: 131.78 ± 11.83 mm Hg, p = 0.0000001).
2. Significant decrease of DBP (Mean ± SD: I study: 93.58 ± 7.71 vs II study: 74.17 ± 10.03 mm Hg, p = 0.0000001).
3. Non-significant decrease of ET-1 conc. (Median ± S I study: 83.3 ± 23.9 vs II study: 78.7 ± 20.85 pg/ml, p = = 0.102).
4. Non-significant increase of Ald conc. (Median ± S I study: 125.9 ± 66.53 vs II study: 158.49 ± 76.15 pg/ml, p = 0.52).

Conclusion 30-day treatment of essential hypertensive patients with amlodipine in dose 5 mg/day induced a non-significant decrease of ET-1 concentration, which may be important for the therapeutic use of amlodipine in everyday practice. However, it should be also noted that our data were collected from a relatively small group of patients (39), and probably need to be confirmed in larger population sample.

key words: endothelin-1, amlodipine, essential hypertension, calcium antagonists

Arterial Hypertension 2011, vol. 15, no 1, pages 5–12

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