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PRACA ORYGINALNA

The influence of losartan and trandolapril therapy on serum glucose, insulin, homocysteine and von Willebrand factor in mild to moderate essential hypertension

Wpływ terapii losartanem i trandolaprilem na glukozę, insulinę, homocysteinę oraz czynnik von Willebranda u chorych z pierwotnym łagodnym do umiarkowanego nadciśnieniem tętniczym

Streszczenie

Wstęp W pierwotnym nadciśnieniu tętniczym zaburzenia gospodarki węglowodanowej (ZW) często współistnieją z zaburzeniami funkcji śródbłonka naczyń (ED).

Materiał i metody Celem pracy była ocena wpływu antagonisty receptora AT_1 — losartanu 50 mg/dz. — oraz inhibitora ACE — trandolaprilu 2 mg/dz. — na zaburzenia gospodarki węglowodanowej i dysfunkcję śródbłonka w pierwotnym, dotychczas nieleczonym nadciśnieniu tętniczym. We krwi na czczo oceniano: glukozę, insulinę, całkowitą homocysteinę, HbA_{1c}, kwas moczowy, czynnik von Willebranda (vWF:Ag) oraz HOMA-IR, BMI, WHR u chorych z nadciśnieniem łagodnym do umiarkowanego w porównaniu z grupą odpowiednią kontrolną. Ocena została powtórzona w obu leczonych grupach po 3 miesiącach

Wyniki W obu leczonych grupach, poza obniżeniem wartości ciśnienia, uzyskano także obniżenie stężenia HbA_{1c}, co sugeruje korzystny wpływ farmakoterapii na (ZW). Stwierdzono obniżenie vWF:Ag w grupie losartanu i wzrost vWF:Ag w grupie trandolaprilu. Różny wpływ na vWF:Ag (traktowany jako marker uszkodzenia śródbłonka) można tłumaczyć poprzez odmienny mechanizm ingerencji badanych leków na układ RAA oraz przez prawdopodobny udział układu kinin, których aktywność jest wzmożona w trakcie terapii inhibitorem ACE. Grupa trandolaprilu cechowała się wyższym wskaźnikiem talia-biodra (WHR) w porównaniu z grupą kontrolną (niż grupa losartanu), co może sugerować występowanie poważniejszych ZW, spowodowanych zwiększoną ilością tkanki tłuszczowej brzusznej. Grupa trandolaprilu miała wyższe stężenia glukozy, HbA_{1c}, całkowitej homocysteiny niż grupa losartanu w porównaniu z grupą kontrolną (przed leczeniem).

Wnioski Dane autorów sugerują, że grupa chorych z łagodnym do umiarkowanego nadciśnieniem tętniczym, chociaż klinicznie podobna, może w różny sposób odpowiadać na farmakoterapię, co może być efektem stopnia zaawansowania zaburzeń metabolicznych występujących jeszcze przed leczeniem.

słowa kluczowe: HbA_{1c}, pierwotne nadciśnienie tętnicze, losartan, trandolapril, czynnik von Willebranda

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Introduction

Essential arterial hypertension (EH) is an important cause of nephropathy and chronic renal failure and so remains a medical and economic problem for society. Contemporary EH treatment focuses on many aspects, especially on making a positive impact on metabolic disturbances and impaired endothelial function [1]. The carbohydrate metabolism disturbances (CM) observed in EH patients are conducive to endothelial dysfunction (ED), signifying an imbalance between vasodilation and vasoconstriction.

ED is considered to be a crucial initial step in the progression of atherosclerosis and hyperhomocysteinaemia is believed to be a risk factor in this process [2]. ACE inhibitors occupy a prominent position in the therapy of EH, although angiotensin II receptor 1 (AT_1) antagonists attract much attention. The role of ACE inhibitors is to block the tissue and systemic renin-angiotensin-aldosterone systems. The inhibition of angiotensin I to II enzymatic conversion and the prevention of bradykinin degradation result in the positive clinical effects of ACE inhibitors. The significant importance of the increased bradykinin tissue amount has been understood recently. This vasodilator peptide influences the vascular endothelium, stimulating arachidonic acid metabolism, which increases prostacyklin biosynthesis. Another positive effect of higher bradykinin levels is the increase in nitric oxide (NO) production [3].

On the other hand the AT_1 receptor antagonists which bind selectively to the angiotensin II AT_1 receptors inhibit the biological function of angiotensin II and increase its serum concentration. In this way more angiotensin II interacts with the second class of its receptors, AT_2, which results in elevated NO production and vasodilatation [4]. The aim of this study, therefore, was to compare ACE inhibitor trandolapril and AT_1 antagonist losartan monotherapy as regards metabolism, mainly CM and ED, in previously non-treated mild to moderate EH patients.

Material and methods

A comparison was made between 25 non-microalbuminuric at baseline, non-diabetic (on the basis of fasting glucose level) ambulatory patients with untreated EH (11F/14M) staged, according to WHO, at phases I or II and 14 controls (7F/7M) matched for age. The EH patients were divided into two groups. Group A: 12 patients (5F/7M) were given AT_1-antagonist losartan in a dose of 50 mg. Group B: 13 patients (7F/6M) were given ACE inhibitor trandolapril in a dose of 2 mg. The drugs were given for 3 months. Before and after the 3-month therapy the following samples were collected: 24h urine for albumin excretion and N-acetyl-β-D-glucosaminidase (NAG), creatinine and fasting blood for insulin, glucose, homocysteine, glycated haemoglobin (HbA_{1c}) and uric acid. The study protocol was approved by the Ethics Committee at The Ludwik Rydygier Medical University, Bydgoszcz. Written informed consent was obtained from all the patients.

NAG was measured with a colorimetric assay using a Boehringer Mannheim reagent kit (3-cresolsulfonphtaleinyl-N-acetyl-β-D-glucosaminidase sodium salt as a substrate). The results were corrected for creatinine urine concentration. Microalbuminuria was measured by a turbidimetric method (Dade Behring) on a Turbitimer analyser. Total homocysteine was measured on an IMX analyser (Fluororescence Polarisation Immunoassay FPIA-Abbott Laboratories). Insulin was measured on an AxSym analyser (Microparticle Enzyme Immunoassay-MEIA, Abbott Laboratories). The content of glycated haemoglobin A1c (%) was calculated on an IMX analyser (MEIA technology, Abbott Laboratories). Glucose levels (enzymatic test, Roche) and creatinine levels (Jaffé method, Roche) were measured on a Hitachi 912 analyser. Insulin resistance was evaluated by the homeostasis model assessment (HOMA-IR), which was calculated from: HOMA-IR = fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/l)/22.5. Uric acid was measured on a Hitachi 912 analyser by the BioMerieux immunoenzymatic method. The von Willebrand Factor was measured by the immunoenzymatic method using anty-vWF:Ag antibodies (IgG) from Dako, Denmark. The results were shown in percentages of the vWF:Ag activity in referential serum.

Arterial blood pressure was measured by the Korotkow method (phases I and V) with a standardised mercury sphygmomanometer, the patients having been in the sitting position for 5 minutes. MAP (mean arterial pressure) was calculated as diastolic blood pressure plus 1/3 pulse pressure. WHR (waist to hip ratio) and BMI (body mass index) were calculated. The results are expressed as a mean ± standard deviation when normal distribution is found. Data without normal distribution is presented as median and range. The Statistica 5 program was used to perform the statistical analysis. A $p < 0.05$ was considered to be statistically significant. The SN abbreviation was used to represent no significance. The significance of differences between means of measurements for two groups was determined by Student's test or the Cochran-Cox test for paired data after an analysis of variances by the Fisher test. Also the U-Mann-Whitney non-parametric test was used for unpaired data without normal distribution. Pearson's correlation coefficients were performed to assess linear relationship.

Results

Patients of group B were distinguished by higher WHR, HbA_{1c}, glucose and homocysteine in comparison with the controls, while the patients in group A did not differ from the controls in this respect (tab. I, II). However, it must be emphasised that when a comparison between groups A and B was made (tab. III), group B was characterised by lower vWF:Ag and higher fasting glucose before treatment only. The other parameters measured did not differ between groups A and B. Tables IV and V show the effects of both losartan and trandolapril therapy on the parameters calculated. In both groups MAP and HbA_{1c} fell to the same extent during therapy. Although losartan therapy lowered vWF:Ag, the trandolapril group showed the opposite effect on vWF:Ag. Before therapy the following linear correlation was found exclusively in group A: vWF:Ag vs. glucose ($r = -0.63$; $p < 0.05$) while in group B the following were found: HbA_{1c} vs. insulin ($r = 0.57$; $p < 0.05$) and HbA_{1c} vs. HOMA-IR ($r = 0.61$; $p < 0.05$). No other linear correlation was found in either group, either before or after therapy. There was no significant difference in albuminuria (mg/24 h) between groups A and B (13.62 ± 6.30 vs. 16.06 ± 7.68; pNS), between these groups and the controls (16.18 ± ± 15.13; pNS) and no significant change of albuminuria was noticed in groups A and B after treatment.

Discussion

During the 3-month treatment there were no adverse events in either group of patients. Hyperinsulinemia, elevated HOMA-IR, hyperglycaemia and increased HbA_{1c} may suggest the presence of insulin resistance in the patients in the present study and this is in agreement with others [5]. The hyperinsulinaemia found in EH may indirectly lower uric acid excretion, which may explain the hyperuricaemia in our patients. However the possibility cannot be excluded that the intrarenal vessel damage found in EH may contribute to a lowering of uric acid urine excretion. The EPIC-Norfolk study proved that HbA_{1c} is an in-

Table I. Characteristics of patients in group A and B before treatment comparing to controls
Tabela I. Charakterystyka pacjentów grup A i B przed leczeniem w porównaniu z grupą kontrolną

Parameter	Group A vs. controls	p	Group B vs. controls	p	Controls
Age (years)	39.50 ± 12.63	NS	44.77 ± 12.17	NS	40.07 ± 11.18
BMI	28.33 ± 4.80	< 0.05	28.54 ± 4.21	< 0.01	23.07 ± 2.43
WHR	0,91 ± 0,11	NS	0.90 ± 0.08	< 0.05	0.83 ± 0.10
MAP [mm Hg]	124 ± 8.5	< 0.01	127 ± 9.61	< 0.01	84 ± 10.5
Systolic blood pressure [mm Hg]	164 ± 14.4	< 0.01	167 ± 6.93	< 0.01	115 ± 14.3
Diastolic blood pressure [mm Hg]	104 ± 6.9	< 0.01	106 ± 6.9	< 0.01	68 ± 9.0

WHR, waist/hip ratio, MAP, mean arterial pressure, BMI, body mass index

Table II. Characteristics of patients in group A and B before treatment comparing to controls
Tabela II. Charakterystyka pacjentów grup A i B przed leczeniem w porównaniu z grupą kontrolną

Parameters	Group A vs. controls	p	Group B vs. controls	p	Controls
HbA_{1c} (%)	6.01 (4.96–6.85)	NS	6.09 (5.22–6.73)	< 0.05	5.66 (4.73–7.63)
Insulin [μU/mL]	13.74 ± 7.57	< 0.01	11.37 ± 5.86	< 0.01	6.87 ± 2.10
Glucose [mmol/L]	5.17 ± 0.56	NS	5.66 ± 0.41	< 0.05	5.08 ± 0.41
HOMA-IR	3.17 ± 1.71	< 0.01	2.89 ± 1.61	< 0.05	1.59 ± 0.53
Uric acid [μmol/L]	377 ± 93	< 0.01	328 ± 81	< 0.05	263 ± 71
Homocysteine [μmol/L]	8.83 ± 3.05	NS	10.49 ± 2.53	< 0.05	8.39 ± 2.55
NAG [IU/g creat]	1,89 (1.24–7.45)	NS	2.68 (1.00–10.6)	NS	1.29 (0.25–5.89)
vWF:Ag (%)	267 (130–490)	< 0.01	130 (39–264)	< 0.05	95 (71–120)

HOMA-IR, insulin resistance homeostasis model assessment

Table III. Characteristics of patients in group A and B before treatment
Tabela III. Porównanie pacjentów grup A i B przed leczeniem

Parameter	Group A	Group B	p
Age (years)	39.50 ± 12.63	44.77 ± 12.17	NS
BMI	28.33 ± 4.80	28.54 ± 4.21	NS
WHR	0.91 ± 0.11	0.90 ± 0.08	NS
MAP [mm Hg]	124 ± 8.5	127 ± 9.61	NS
Insulin [μU/mL]	13.74 ± 7.57	11.37 ± 5.86	NS
Glucose [mmol/L]	5.17 ± 0.56	5.66 ± 0.41	< 0.05
HOMA-IR	3.17 ± 1.71	2.89 ± 1.61	NS
Uric acid [μmol/L]	377 ± 93	328 ± 81	NS
Homocysteine [μmol/L]	8.83 ± 3.05	10.49 ± 2.53	NS
NAG [IU/g creat]	1.89 (1.24–7.45)	2.68 (1.00–10.6)	NS
vWF:Ag (%)	267 (130–490)	130 (39–264)	< 0.01

WHR, waist/hip ratio, MAP, mean arterial pressure, BMI, body mass index

Table IV. The characteristics of group A before [I] and after [II] Losartan therapy
Tabela IV. Charakterystyka pacjentów grupy A przed [I] i po [II] leczeniu losartanem

Parameters	Group A [I]	Group A [II]	P
MAP [mm Hg]	124 ± 8.5	100 ± 7.1	< 0.01
HbA_{1c} (%)	6.01 (4.96–6.85)	5.84 (4.67–6.54)	< 0.05
Insulin [μU/mL]	13.74 ± 7.57	12.66 ± 7.38	NS
Glucose [mmol/L]	5.17 ± 0.56	5.45 ± 0.84	NS
HOMA-IR	3.17 ± 1.71	3.25 ± 2.33	NS
Uric acid [μmol/L]	377 ± 93	368 ± 86	NS
Homocysteine [μmol/L]	8.83 ± 3.05	9.93 ± 2.37	NS
NAG [IU/g creat]	1.89 (1.24–7.45)	2.86 (0.75–6.71)	NS
vWF:Ag (%)	267 (130–490)	145 (48–384)	< 0.02

HOMA-IR, insulin resistance homeostasis model assessment

Table V. The characteristics of group B before [I] and after [II] Trandolapril therapy
Tabela V. Charakterystyka pacjentów grupy B przed [I] i po [II] leczeniu trandolaprilem

Parameters	Group B [I]	Group B [II]	p
MAP [mm Hg]	127 ± 9.61	97 ± 6.03	< 0.001
HbA_{1c} (%)	6.09 (5.22–6.73)	5.68 (5.09–6,40)	< 0.05
Insulin [μU/mL]	11.37 ± 5.86	11.06 ± 6.55	NS
Glucose [mmol/L]	5.66 ± 0.41	5.43 ± 0.41	NS
HOMA-IR	2.89 ± 1.61	2.65 ± 1.52	NS
Uric acid [μmol/L]	328 ± 81	334 ± 11	NS
Homocysteine [μmol/L]	10.49 ± 2.53	10.74 ± 2.55	NS
NAG [IU/g creat]	2.68 (1.00–10.6)	2.33 (0.56–4.63)	NS
vWF:Ag (%)	130 (39–264)	276 (90–547)	< 0.01

HOMA-IR, insulin resistance homeostasis model assessment

dependent cardiovascular disease risk factor and a predictor of cardiovascular as well as all other causes of death in diabetic and non-diabetic populations [6]. The HbA_{1c} is generated as a result of non-enzymatic protein glycation which occurs during hyperglycaemia. There was a significant decrease in HbA_{1c} level after the 3-month treatment in both groups in our study. This desirable result suggests a decrease in protein glycation and, probably, a lessening of ED. After trandolapril therapy the positive linear associations between HbA_{1c} and insulin and HOMA-IR were no longer observed. This is a positive influence of ACE inhibitor on CM and is due to the probable increase of tissue insulin sensitivity as evidenced by the fact that the fasting glucose decreased to the level observed in the controls. There was no such linear association in the group treated with losartan.

It seems that AT_1 antagonists may affect glycation differently from ACE inhibitor, although the difference between the groups treated cannot be overlooked. Group B had higher WHR than Group A in comparison with the controls, which suggests the possibility of more severe metabolic disturbances due to increased abdominal adipose tissue deposit. Compared to the controls Group B was characterised by higher glucose, HbA_{1c}, homocysteine and lower vWF:Ag than group A before treatment. The lowering of HbA_{1c} in the group treated with trandolapril in the face of no change in HOMA-IR and the vanishing of positive linear correlations between HbA_{1c} and insulin and HOMA-IR after treatment could be interpreted as a pathogenic association between insulin resistance and protein glycation. It seems that in this case ACE inhibitors affect the glycation process without any influence on insulin sensitivity. It is known that the positive metabolic effect of ACE inhibitors results from decreased bradykinin degradation. Bradykinin may affect glucose metabolism through the increase in its peripheral tissue uptake, a decrease in endogenous glucose production and an increase in glycolysis [7]. The HOPE and CAPPP studies showed the desirable effects of ACE inhibitor on insulin sensitivity, although this was not confirmed in the STOP-2 trial [8]. Data concerning trandolapril and carbohydrate metabolism disturbances in non-diabetic patients is ambiguous. The TRIS study showed a decrease in insulin resistance in obese hypertensives treated with trandolapril [9]. This was not confirmed in the study on an EH non-diabetic group which did not reveal any impact of trandolapril on glucose or on insulin resistance [10]. A direct comparison of trandolapril and losartan showed a superiority in the ACE inhibitor influence on insulin resistance in postmenopausal hypertensive women [11]. A significant improvement in insulin sensitivity was demonstrated for losartan in other studies with severe hypertensives, probably due to the decrease in sympathetic system activity [12]. Recent data [13] has shown that both ACE inhibitors and AT_1 antagonists lower *in vitro* formation of AGE (advanced glycation end products), which may partially explain the HbA_{1c} decrease in our study.

We consider vWF:Ag, one of the endothelium-derived adhesive glycoproteins, to be an ED and damage marker [14]. vWF:Ag alone is recognised and used to determine endothelial status in EH [15], although the addition of selectins, VCAM-1 or ICAM-1 might be useful because vWF:Ag is also an acute phase reactant. vWF:Ag is constitutively secreted to plasma as well as stored and released by means of exocytosis from the secretory granules of endothelium known as the Weibel-Palade bodies. It plays a role in primary haemostasis but its increased level is associated with clotting, a prothrombotic state and a higher cardiovascular risk, as has been shown in ARIC, ECAT and other studies [16, 17]. In addition to the lowering of HbA_{1c} and MAP in both groups in our study, there was a difference in vWF:Ag change after treatment. The vWF:Ag level showed, as desired, a decrease in the group treated with losartan but an increase in the trandolapril group. This phenomenon is in disagreement with data showing a positive association between vWF:Ag and insulin resistance in non-diabetic EH [18]. There is also data concerning the lack of ACE inhibitor influence on vWF:Ag in normotensive diabetic patients and healthy volunteers [19].

No change in vWF:Ag was found in EH after 8 weeks of losartan treatment [14]. Although losartan has uricosuric properties (due to the inhibition of uric acid proximal tubule reabsorption), there was no uric acid level change after losartan therapy. In this case, therefore, the lowering of vWF:Ag in group A cannot be explained by uric acid level correction. We suppose that the different influence of losartan and trandolapril on vWF:Ag in our study might be the result of metabolic differences found at the start between the groups treated. This means that even clinically similar hypertensive patients may respond to therapy in different ways. Beyond any doubt the weakness of this study was that it was not randomised and that it lacked cross-over design. Instead the sole purpose was to compare the effect of two drugs in patients who on a clinical basis were similar. The similarity between them (in respect of age, blood pressure and BMI) blurred the metabolic disturbance differences. Patients randomly allocated to losartan therapy revealed differences in HbA_{1c}, homocysteine and vWF:Ag when compared to the controls.

Conclusions

AT_1-antagonist losartan and ACE-inhibitor trandolapril in monotherapy corrected impaired glucose metabolism (assessed by a decrease in HbA_{1c} level) besides lowering blood pressure in overweight mild to moderate EH patients. AT_1-antagonist losartan had a beneficial effect on ED (as assessed by a decrease in vWF:Ag level), which may emphasise the influence of CM and oxidative stress on endothelium in EH. A group of mild to moderate EH patients, while clinically similar, may respond in different ways to the treatment process, which may be a result of the severity of the metabolic disturbances found in this group.

Abstract

Background Carbohydrate metabolism disturbances (CM) and endothelial dysfunction (ED) often coexist with essential arterial hypertension (EH).

Material and Methods In order to investigate the effect of AT_1-antagonist losartan in a daily dose of 50 mg and ACE-inhibitor trandolapril in a daily dose of 2 mg on CM and ED in untreated EH the following were evaluated in mild to moderate EH patients during fasting: glucose, insulin, total homocysteine, HbA_{1c}, uric acid, von Willebrand Factor (vWF:Ag), HOMA-IR, BMI and WHR and the results compared to those for matched controls. The examination was repeated after 3 months in both the groups treated.

Results A decrease in HbA_{1c} in both groups treated suggests CM correction besides the lowering of blood pressure. There was a decrease in the vWF:Ag level in the losartan group and an increase in the vWF:Ag level in the group treated with trandolapril. This difference in vWF:Ag (known as an ED marker) may be explained by the distinct way in which the drugs under examination influenced the renin-angiotensin--aldosterone system and by the possible role of kinins, the activity of which is elevated during ACE--inhibitor treatment. The trandolapril group had a higher WHR than the losartan group when compared to controls, which implies the possibility of more severe CM due to increased abdominal adipose tissue deposit. It was also characterised by higher fasting glucose, HbA_{1c}, total homocysteine than the losartan group when compared to controls before treatment.

Conclusions Our data may suggest that mild to moderate EH patients, even when clinically similar, may respond differently to drug treatment, which may be the result of the severity of the metabolic disturbances found in this group at the beginning of treatment.

key words: HbA_{1c}, essential hypertension, losartan, trandolapril, von Willebrand Factor

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