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ENDOTHELIUM-DEPENDENT MECHANISMS OF NEPHROPROTECTIVE EFFECT OF RENIN-ANGIOTENSIN SYSTEM MODULATORS IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Abstract

Introduction. It has been shown that essential hypertension (EH) is one of the main causes of end-stage renal failure in 10-30% of patients on programmed hemodialysis. At the same time, according to some clinical studies, it was shown that the most widely used drugs (diuretics, beta-blockers, calcium channel antagonists, etc.) effectively reduce high blood pressure (BP), are able to prevent the development of myocardial infarction and cerebral catastrophes, however, do not have a sufficient nephroprotective effect.

The aim of the study is to identify the nephroprotective efficacy of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists in patients with EH.

Materials and methods of research. To achieve this goal, 40 patients with stage I-II EH with a level of I-III degree of arterial hypertension at the age of 34 to 63 years (mean age 45.8±1.14

years) were examined, without adequate systematic antihypertensive therapy, in which, as a result of a complex clinical-anamnestic and instrumental-laboratory research, there were no data which can indicate on the presence of manifest hypertensive nephropathy and other clinically significant expressed signs of chronic kidney diseases.

Research results. Evaluation of the obtained results showed that patients of both groups had a significant antihypertensive effect: the decrease in systolic BP and diastolic BP at the end of the course of therapy in patients of group 1 was 18.24% and 15.67%, in the group 2 was 17.32% and 15.44 %, respectively. The dynamics of urinary albumin excretion at the end of the course of therapy was also found to be reliable in comparison with the primary data: in the treatment with enalapril the level of albuminuria decreased by 25.13%, excretion of β 2-microglobulin decreased by 18.82%. In group 2, the decrease in these indicators was 16.34% and 17.46%, respectively ($p < 0.05$). It should be noted a statistically significant decrease in glomerular permeability index, an indirect marker of intraglomerular hypertension: for patients in group 1 by 19.14%, for patients in group 2 by 14.12%, respectively. Evaluation of the effectiveness of the treatment on the functional state of the kidneys in the examined patients with EH showed that in 19 patients (82.61%) of the 1st group and in 15 patients (68.18%) of the 2nd group, therapy was regarded as effective.

Conclusions. Therapy with enalapril and irbesartan has a significant antihypertensive and nephroprotective effect. Evaluation of indicators characterizing the functional state of the kidneys in patients with essential hypertension during therapy indicates that enalapril has a more pronounced nephroprotective effect in comparison with irbesartan. The effectiveness and rationality of nephroprotective therapy is largely determined by the positive dynamics in the reserve capacity of the kidneys and in the restoration of the functioning of the vascular endothelium.

Key words: intraglomerular hypertension; renal functional reserve; hypertensive nephropathy.

Introduction. It has been shown that essential hypertension (EH) is one of the main causes of end-stage renal failure in 10-30% of patients on programmed hemodialysis [1]. At the same time, according to some clinical studies, it was shown that the most widely used drugs (diuretics, beta-blockers, calcium channel antagonists, etc.) effectively reduce high blood pressure (BP), are able to prevent the development of myocardial infarction and cerebral catastrophes, however, do not have a sufficient nephroprotective effect [2]. The data of numerous clinical and experimental studies and observations suggest that the nephroprotective effect is more pronounced in angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, in contrast to other antihypertensive drugs [3]. However, the results of recent studies, which confirmed that bradykinin, the degradation of

which is blocked by ACE inhibitors, does not make a significant contribution to the systemic hemodynamic effects caused by ACE inhibitors, it becomes clear that there is a tendency to identify the systemic cardiovascular effects of ACE inhibitors and angiotensin II receptor antagonists [4]. However, regional, in particular, renal, blood flow is characterized by patterns other than central circulation, which may determine the peculiarities of the influence of drugs of these groups on the parameters characterizing the functional state of the kidneys in EH [5]. This work is devoted to the study of this aspects.

The aim of the study is to identify the nephroprotective efficacy of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists in patients with EH.

Materials and methods of research. To achieve this goal, 40 patients with stage I-II EH with a level of I-III degree of arterial hypertension at the age of 34 to 63 years (mean age 45.8 ± 1.14 years) were examined, without adequate systematic antihypertensive therapy, in which, as a result of a complex clinical-anamnestic and instrumental-laboratory research, there were no data which can indicate on the presence of manifest hypertensive nephropathy and other clinically significant expressed signs of chronic kidney diseases. The patients underwent 24-hour blood pressure monitoring (ambulatory blood pressure monitoring, ABPM) using a CardioTens-01 recorder (Meditech, Hungary) according to the standard protocol. The vasomotor function of the endothelium was assessed using a Sonoline Versa Plus ultrasound apparatus (SIEMENS, Germany). The change in the internal diameter of the brachial artery (the value of endothelium-dependent vasodilation, EDVD) was calculated as a percentage of the diameter obtained after temporary compression in comparison with the baseline value. Functional renal reserve (FRR), a clinical marker of intraglomerular hyperfiltration, was assessed for all subjects using the indicators of basal and stimulated glomerular filtration rate based on endogenous creatinine clearance when performing an oral protein test in an adequate water regime. The concentration of creatinine was determined by a standardized method using the Jaffe color reaction (Popper method). The calculation of the glomerular permeability index (GPI), which reflects the average concentration of albumin in the glomerular ultrafiltrate, was carried out. Evaluation of the effectiveness of the effect of therapy on the functional state of the kidneys was carried out according to the patented original method.

The level of excretion of albumin and β 2-microglobulin (B2M) with urine were investigated using kits from ORGenTec GmbH, (Germany) according to the attached instructions on a semi-automatic analyzer "DigiScan" Asys Hitech (Austria) on the basis of the Training Medical and Laboratory Centre of Zaporizhia State Medical University, certified by the Ministry of Health of Ukraine (certificate № 039/14). The state of renal hemodynamics was studied in a horizontal position of the patient on the above apparatus, using color Doppler mapping and pulsed wave Doppler with a

convex probe. The blood flow in the renal arteries was studied at the level of the segmental and interlobar branches of the renal arteries (SRA and IRA) in the spectral Doppler mode, assessing the linear blood flow parameters: peak systolic velocity (PSV), maximum end-diastolic blood flow velocity (EDV), time averaged maximum velocity (TAMX). The indicators of peripheral vascular resistance were also used: diastolic-systolic velocity ratio (DSVR), PI – pulsation index, RI – resistance index (peripheral vascular resistance). The calculations were carried out automatically when processing the Doppler curves using the appropriate formulas.

On average in the group of patients, systolic blood pressure (SBP) was 166.96 ± 2.62 mm Hg, diastolic blood pressure (DBP) – 104.14 ± 2.09 mm Hg. At the time of inclusion in the study, patients did not receive systematic adequate antihypertensive therapy. All patients were divided into 2 groups (22 and 18 people, respectively). The groups did not differ in gender, age and clinical features of the disease. After the initial examination, all patients in group 1 were prescribed monotherapy, including the ACE inhibitor enalapril (Enap, KRKA), patients in group 2 received an angiotensin II receptor antagonist irbesartan (Aprovel, Sanofi-Aventis). The doses of enalapril and irbesartan were titrated to achieve the target dose of enalapril 40 mg / day and irbesartan 150 mg / day, or the maximum tolerated dose that provides an adequate degree of blood pressure reduction. In cases where monotherapy with drugs was not enough to achieve the target blood pressure level (observed in 13.04% of patients in group 1 and 9.09% in group 2), combination therapy with an individual selection of drugs were prescribed, according to modern recommendations, but for further statistical analysis the results these patients were not included. After the end of the titration period, the average dose of enalapril in the group of patients was 24.18 ± 1.23 mg / day, of irbesartan – 115.92 ± 9.03 mg / day. 3 months after the end of the dose titration period, a repeated study was carried out, including the assessment of indicators characterizing the functional state of the kidneys.

All statistical procedures were performed using the STATISTICA® for Windows 6.0, SPSS 16, and Microsoft Excel 2018 software packages.

Research results and their discussion. Evaluation of the obtained results showed that patients of both groups had a significant antihypertensive effect: the decrease in SBP and DBP at the end of the course of therapy in patients of group 1 was 18.24% and 15.67%, in the group 2 was 17.32% and 15.44 %, respectively.

Covariance analysis of the results of the study showed that patients of the 1st group, in addition to the comparable achieved antihypertensive effect, were characterized by more pronounced dynamics in terms of the FRR, urinary microprotein excretion and the frequency of reversal of the presence of subclinical kidney damage (the frequency of detection of microalbuminuria). The dynamics of the FRR also revealed statistically significant, differing only in the magnitude of the

differences. So, against the background of therapy with enalapril, the difference between the initial FRR data and after treatment was + 49.14%, for irbesartan + 37.21% ($p < 0.01$). The dynamics of urinary albumin excretion at the end of the course of therapy was also found to be reliable in comparison with the primary data: in the treatment with enalapril the level of albuminuria decreased by 25.13%, excretion of B2M decreased by 18.82%. In group 2, the decrease in these indicators was 16.34% and 17.46%, respectively ($p < 0.05$). It should be noted a statistically significant decrease in GPI, an indirect marker of intraglomerular hypertension: for patients in group 1 by 19.14%, for patients in group 2 by 14.12%, respectively.

Evaluation of the effectiveness of the treatment on the functional state of the kidneys in the examined patients with EH showed that in 19 patients (82.61%) of the 1st group and in 15 patients (68.18%) of the 2nd group, therapy was regarded as effective. From this point of view, indicative of the results of analysis of variance using a two-factor scheme with repeated measures, during which the dynamics of microalbuminuria was assessed at different periods of treatment against the background of therapy with enalapril or irbesartan. The obtained results indicated that therapy with enalapril was characterized by a greater, than irbesartan, effect on a decrease in urinary albumin excretion ($F = 4.94$, $p = 0.034$). Considering the presented data, it can be concluded that enalapril had a more pronounced nephroprotective effect, despite a similar antihypertensive effect, which is probably associated with a more favorable effect on renal hemodynamics, both due to the effect on the metabolism of effector peptides of the renin-angiotensin system and potentiation of the effects of activation the kallikrein-kinin system mediated by bradykinin [6, 7].

Multivariate analysis of variance with repeated measurements (during therapy) and the F-ratio indicated a significant effect of the class of drug (intergroup factor), the severity of endothelial dysfunction and renal hemodynamic disorders on the level of albumin excretion in the urine during therapy. In turn, the normalization of intrarenal hemodynamics, restoration of the functional state of the vascular endothelium and a decrease in the phenomena of intraglomerular hypertension were the main determinants, causing a decrease in the excretion of microalbumin and beta-2-microglobulin in the urine. Summarizing the above data, we can also conclude that the presence of impairments in the renal reserve in proportion to increase glomerular filtration (intraglomerular hypertension) is an important clinical predictor of both the formation of nephropathy in hypertension and the effectiveness of antihypertensive therapy.

Conclusions:

1. Therapy with enalapril and irbesartan has a significant antihypertensive and nephroprotective effect.

2. Evaluation of indicators characterizing the functional state of the kidneys in patients with essential hypertension during therapy indicates that enalapril has a more pronounced nephroprotective effect in comparison with irbesartan.

3. The effectiveness and rationality of nephroprotective therapy is largely determined by the positive dynamics in the reserve capacity of the kidneys and in the restoration of the functioning of the vascular endothelium.

Prospects for further research. A promising goal of future studies is to assess the effect of combination therapy with inhibitors of the renin-angiotensin system on the state of intrarenal hemodynamics and the functional state of the kidneys.

Conflicts of interest. Neither author has actual or potential conflicts of interest.

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