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ASSESSMENT OF THE EFFECT OF RAMIPRIL ON THE ARTERIAL BLOOD PRESSURE LEVEL, THE SEVERITY OF PROTEINURIA, AND THE FUNCTIONAL STATE OF THE KIDNEYS IN PATIENTS WITH STAGE II CHRONIC KIDNEY DISEASE (CKD)

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At the end of 2004 in the world, 1,783,000 patients with end-stage chronic kidney disease (CKD) were registered. 1,371,000 (77%) of them received dialysis treatment and 412,000 (23%) underwent kidney transplantation [15]. The increase in the number of patients requiring an expensive substitution therapy has led to serious economic and organizational problems in most countries of the world [1, 5]. The study of the pathogenetic mechanisms of CKD aggravation made it possible to establish a chain of causes for renal function deterioration, such as arterial hypertension (AH), proteinuria, diabetes mellitus (DM), an increase in creatinine levels and a decrease in glomerular filtration rate (GFR) [2, 3, 4, 6, 15]. Identification of the mechanism of CKD aggravation made it possible to develop new approaches to the treatment of such patients using drug and non-drug therapy. This has led to a decrease in the frequency of complications and the CKD aggravation rate and contributed to the lengthening of the pre-dialysis period and, accordingly, a significant reduction in the financial costs of society [1] .

Adequate antihypertensive therapy can slow down and delay the onset of chronic renal failure (CRF) [2]. In addition to lowering blood pressure (BP), the elimination of intraglomerular hypertension is very important for the prevention of nephrosclerosis. Antihypertensive drugs that can reduce intraglomerular hypertension have a more significant nephroprotective effect than those that do not affect intraglomerular hypertension [6, 9]. According to some observations, renal functions during antihypertensive therapy are more stable in those patients, who have a decrease in intraglomerular pressure in the first days of treatment with antihypertensive drugs. This decrease in intraglomerular pressure is clinically manifested by a transient decrease in glomerular filtration rate [4].

A decrease in proteinuria also has a renoprotective effect [2, 11, 17]. The kidney function deterioration occurs more rapidly in patients with severe proteinuria. On the contrary, the decrease in proteinuria at the beginning of antihypertensive therapy is a predictor of a more favorable course of kidney disease in the future [9, 11]. Proteinuria is the most significant factor that changes the mechanisms regulating the dependence of changes in renal blood flow and glomerular filtration on blood pressure fluctuations. The decrease in proteinuria, regardless of changes in blood pressure in the first 6 months of therapy, is linearly correlated with the level of long-term renal protection: every 50% decrease in daily albuminuria leads to a 45% decrease in the risk of renal failure [2].

Treatment of hypertension in patients with kidney disease does not significantly differ from the generally accepted therapy for high blood pressure [5, 6]. All classes of drugs, usually used for the treatment of arterial hypertension, are acceptable for such patients [7]. However, after the development of CKD, the risk of side effects becomes especially high. On the one hand, this is due to the accumulation of drugs in the circulating blood due to elimination disorders (in those cases when the drug is excreted mainly by the kidneys) [6], on the other hand, antihypertensive therapy can aggravate CKD due to the hemodynamic effect of the drugs: a decrease the volume of circulating blood, low blood pressure, deterioration of renal hemodynamics [5, 6, 7]. This dictates the need for special precautions in the treatment of such patients [7].

One of the priority groups of antihypertensive drugs is angiotensin-converting enzyme inhibitors (ACE inhibitors), which antihypertensive action is based on their ability to suppress the activity of ACE (or kininase II) and, thus, simultaneously affect the functional activity of the reninangiotensin and kallikrein-kinin systems [2, 6, 14, 17]. By inhibiting ACE activity, ACE inhibitors reduce the formation of angiotensin II and, as a result, weaken the main cardiovascular effects of activation of the renin-angiotensin system, including arterial vasoconstriction and aldosterone secretion [6, 9, 16]. ACE inhibitors have a pronounced nephroprotective effect in patients with kidney disease and arterial hypertension, as a result proteinuria reduces and glomerular filtration rate slows down, as well as later morphological changes occur [2, 6].

The main mechanism of kidney protection during treatment with ACE inhibitors is a decrease in hydrostatic pressure in the glomeruli, due to a decrease in the efferent arteriole tone [3, 6]. This prevents protein hyperfiltration and the appearance of morphological changes due to intraglomerular hypertension. The afferent arteriole tone also decreases, but lesser extent than the efferent one. Due to the dilatation of afferent arteriole under the influence of ACE inhibitors, renal blood flow does not worsen, despite a decrease in systemic blood pressure, and urinary protein excretion is significantly reduced [10, 11, 12, 14]. The achieved nephroprotective effect of ACE inhibitors persists for a long time (years) while continuing to take them [2].

The ACE inhibitor group includes a large number of drugs that differ in their pharmacokinetic and pharmacodynamic characteristics significantly. One of the clinically promising ACE inhibitors is ramipril. The drug study results on the hypertension effect have demonstrated an effective decrease in blood pressure, microalbuminuria. The obtained data indicate the ramipril nephroprotective effect (study HOPE; MICRO-HOPE; REIN), associated with a decrease in intraglomerular hypertension, an increase in glomerular filtration rate, sodium excretion and a decrease in potassium, and an increase in total diuresis [5, 13]. ACE inhibitors should be preferred over beta-blockers and dihydropyridine calcium antagonists (AASK study) [5, 10, 11, 12, 13].

OBJECTIVE

To evaluate the effectiveness of ramipril antihypertensive therapy in patients with arterial hypertension caused by stage II CKD and its effect on the level of daily proteinuria and the functional state of the kidneys.

MATERIALS AND METHODS

The study included 30 patients (14 men and 16 women), aged 18 to 50 years (mean 34.2 ± 2.34 years) with stage II CKD (chronic pyelonephritis has been detected in 12 patients (39.96%), chronic glomerulonephritis – in 10 patients (33.3%), type 2 diabetes mellitus – in 5 patients (16.65%), polycystic kidney disease - in 3 patients (9.99%) with glomerular filtration rate (GFR) in the range of 60-90 ml/min (mean GFR 66.02 ± 1.35 ml/min). The diagnosis of CKD and the stage of the disease were made according to the classification approved at the II National Congress of Nephrologists of Ukraine (Kharkiv, 23-24 September 2005) and related changes in the introduction of registers (Order of the Ministry of Health and the Academy of Medical Sciences of Ukraine No. 43/454 dated 10.07.2006) [7, 8].

The inclusion criteria for the study were the presence of verified AH >= 140/90 mmHg, proteinuria > 300 mg/day < 3.5 g/day, GFR >60<90 ml/min, hemoglobin level >= 110 g/l.

Exclusion criteria: hypersensitivity to ramipril or other ACE inhibitors; acute myocardial infarction or cerebrovascular accident in the previous 6 months; severe, refractory hypertension (diastolic blood pressure >110 mmHg and/or systolic blood pressure>=180 mmHg); severe heart failure (according to NYHA III-IV functional class); obstructive uropathy; insulin-dependent diabetes mellitus; tumors; abnormal liver function, increased levels of transaminases: aspartate aminotransferase (AST), alanine aminotransferase (ALT) more than 2 times; hyperkalaemia; confirmed or possible pregnancy; lactation.

For antihypertensive and nephroprotective purposes, patients were treated with ramipril (Cardipril® by Ananta Medicare, UK) in capsules of 2.5 mg once in the morning on an empty stomach. The dose was increased to 5 mg daily under the control of blood pressure with ineffective therapy, after 2 weeks it was additionally combined with hydrochlorothiazide at a dose of 12.5–25 mg/day in the morning. The follow-up period was 4 weeks; the criterion of effectiveness was the achievement of BP <= 130/80 mm Hg, recommended for patients with CKD with a daily proteinuria < 1 g/day and BP <= 125/75 mm Hg at the level of daily proteinuria > 1 g/day.[1]

If a patient received an ACE inhibitor prior to enrollment in the study, he was switched to Cardipril® (ramipril) after a 2-3 day wash-out period. In the absence of achievement of target BP figures against the background of previously prescribed antihypertensive therapy (diuretics 29.9% slow calcium channel blockers - 25.5%, β-blockers - 35%) before inclusion in the study, the patient was considered as having uncontrolled hypertension and Cardipril® (ramipril) was prescribed in addition to this treatment. Basic therapy during the follow-up period did not change and was selected at least 2 weeks before the patient was included in the study and consisted of glucocorticosteroids, uroseptics, and hypoglycemic drugs. The control group consisted of 10 practically healthy individuals matched by sex and age. During the study, the level of blood pressure and heart rate (HR) were monitored. Blood pressure was measured by the Korotkov method in a sitting position after a 5-minute rest. BP was measured again 3 minutes later. If the DBP difference in two measurements was more than 5 mm Hg, an additional measurement was taken and its average value was calculated. The following laboratory tests were used: complete blood count, urinalysis, daily proteinuria measurement, biochemical blood test: creatinine, bilirubin, activity of "liver" enzymes (ALT, AST). GFR was calculated using Cockroft-Gault formula. At the beginning and at the end of the follow-up, a 12-lead ECG was performed to assess the morphofunctional state of the cardiovascular system. The extent to which the patient followed the doctor's instructions was assessed.

The obtained results were statistically processed with the determination of the mean values (M), the mean error (m), and the significance of the difference based on Student's t-test.

RESULTS AND DISCUSSION

In the initial state, the average level of systolic blood pressure was 162.4 ± 5.6 mm Hg, diastolic blood pressure

– 102.6 ± 5.5 mm Hg, heart rate – 77.7 ± 31 beats in minute. The systolic-diastolic variant of AH prevailed in 22 patients (73.3%), and diastolic – in 8 (26.7%), respectively. The study included mainly patients with stage 2 hypertension (< 180/110 mm Hg) – 26 patients (86.7%), stage 1 hypertension (> 140/90 < 160/100 mm Hg) was registered in 4 patients (13.3%).

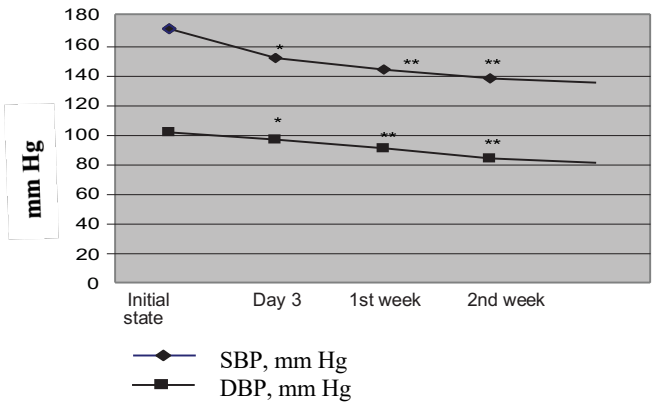
At the end of the follow-up, the target BP level was achieved in 23 patients (76.6%), according to systolic blood pressure – in 24 (78.3%), diastolic blood pressure – in 25 (83.3%) with an average dose of Cardipril® (ramipril) 3.7 ± 0.5 mg/day.

In 54% of cases, the effectiveness of therapy was achieved at a dose of Cardipril® (ramipril) 2.5 mg/day – 13 patients, 5 mg/day – 41%), and in 22.6% – due to combination therapy. During the study, a decrease in systolic blood pressure by 20.4 ± 3.8 mm Hg (p <0.01) and in diastolic blood pressure by 11.6 ± 2.8 mm Hg (p <0.01) with a relative decrease in the parameter by 12.6% and 11.3%, respectively, were reported. No significant change in heart rate was reported. The dynamics of the blood pressure level during the study is shown in Fig.1.

A significant positive effect of Cardipril® (ramipril) on the blood pressure level was observed starting from the Day 3, with the most pronounced effect by the end of the 2nd week. It remains until the end of the observation.

After 4 weeks of using Cardipril® (ramipril), a significant decrease in daily proteinuria was registered from 1.3 ± 0.2 g/day to 0.40 ± 0.06 g/day, which amounted to Δ0.88 ± 0.09 g/day (p<0.01), 81.5% reduction.

Fig. 1. Changes in SBP and DBP during treatment with ramipril (Cardipril® by Ananta Medicare, UK)

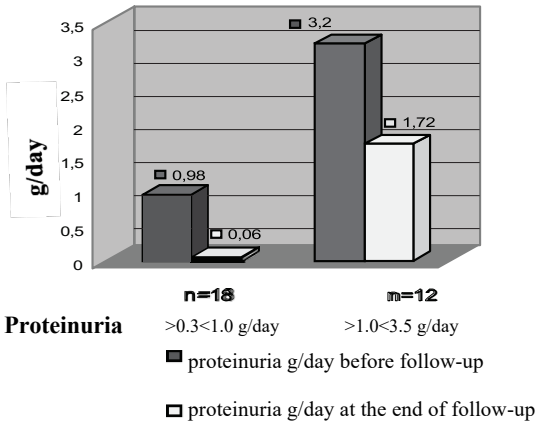


Note: * reliability of differences p<0.01

The obtained results are consistent with the literature data on a significant positive effect of ramipril on proteinuria, the state of vascular endothelial function in patients with diabetes mellitus, arterial hypertension [5, 13].

The positive effect of ACE inhibitors has been found in patients both in the range of 300 mg/day <1 g/day and > 1 g/day <3.5 g/day (Figure 2).

Fig. 2. Reducing proteinuria with ramipril (Cardipril® by Ananta Medicare, UK)



Note: * reliability of differences p<0.01.

A decrease in proteinuria below the threshold level of 300 mg/day was registered in 3 patients (10%), at a level of <1 g/day, and amounted to a decrease in proteinuria by 52.1% (p<0.05), respectively, at a level of> 1<3, 5 g/day – 98.8% (p < 0.01). An increase in daily proteinuria after 4 weeks was not registered in any patient. During the selected follow-up period, no significant changes in the level of serum creatinine and GFR were detected (Fig. 3). ACE inhibitors can increase creatinine levels and decrease GFR in the short term. Therefore, the absence of changes should be assessed as positive for the given follow-up period.

Fig. 3. Dynamics of the effect of ramipril therapy (Cardipril® by Ananta Medicare, UK) on creatinine and GFR

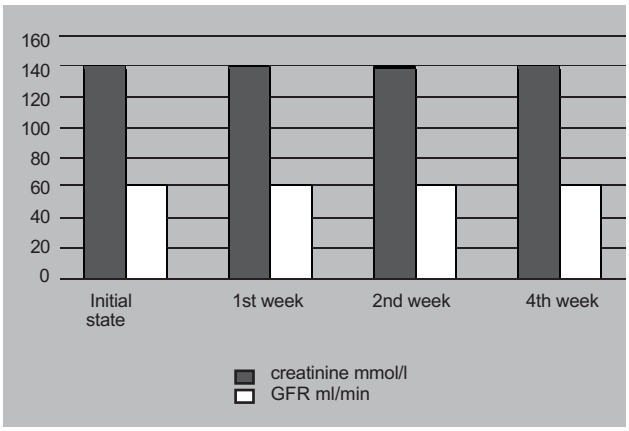


Table 1. Dynamics of biochemical parameters against the background of antihypertensive therapy

Time / Parameters	Initial state	At the end of 4 weeks of follow-up
Hemoglobin, g/l	122.82±2.7	130.63±1.8
Bilirubin, mmol/l	15.4±2.3	16.31±1.8
ALT, U/l	0.45±0.03	0.47±0.04
AST, U/l	0.32±0.05	0.37±0.08
Potassium, mmol/l	4.50±0.08	4.60±0.09
Urea, mmol/l	9.22±4.45	8.89±3.87

A longer period is required to assess the effect of ACE inhibitors on GFR.

There was a positive trend in serum creatinine from 143.6 ± 3.3 mmol/l to 135.5 ± 2.6 mmol/l ($p > 0.05$) and GFR from 66.0 ± 1.4 ml/min to 68.5 ± 1.6 ml/min ($p < 0.05$), respectively.

The drug good tolerability was reported in patients. No clinically significant side effects requiring discontinuation of the drug were reported. The negative dynamics in the complete blood count test (neutropenia), biochemical blood parameters (increased activity of "liver" enzymes (ALT, AST) and potassium levels were also not reported (Table 1).

Thus, Cardipril® (ramipril) by Ananta Medicare (United Kingdom) has demonstrated high antihypertensive efficacy in patients with stage 2 CKD (GFR > 60 ml/min) and the positive effect on the level of proteinuria that confirms the expediency of use in this category of patients.

CONCLUSIONS:

1. Cardipril® (ramipril) by Ananta Medicare (United Kingdom) ensures the achievement of the target level of blood pressure in 76.6% of patients with stage 2 CKD at an average dose of 3.7 ± 0.5 mg/day against the background of good tolerability and safety of the drug.
2. The drug has a nephroprotective effect, which is expressed in a decrease in the level of daily proteinuria with a stable level of creatinine in the blood serum for the selected follow-up period of 4 weeks.

References:

1. «Аналіз десятирічної діяльності і перспективи розвитку нефрологічної допомоги населенню України» Колесник М.О., Сайдакова Н.О., Козлюк Н.І. та ін. //Український журнал нефрології та діалізу.-2008.-1(17).-С.2-10.
2. Багрий А.Е. Новые возможности в лечении диабетической нефропатии// Ліки України.-2008.-№ 9.-С.125-126.
3. Дядык А.И., Багрий А.Э., Зборовский С.Р. Место ингибиторов ангиотензин-превращающего фермента в современной клинической практике // Методические рекомендации. - «Норд-Компьютер».-2005.- 36с.
4. Кутырина И.М., Михайлов А.А. Почка и артериальная гипертензия. Нефрология: Руководство для врачей.// Под ред. И.С. Тареевой. М.: Медицина. -2000- С. 164-188.
5. Лечение артериальной гипертензии с позиций новых (2007) рекомендаций Европейского общества кардиологов//Внутренняя медицина.- 2007.-№ 5.-с.5
6. Моисеев В.С. Ингибиторы АПФ и нефропатия.// Клиническая фармакология и фармакотерапия.-1997.-№4.-С67-69.
7. Наказ МОЗ України № 593 від 12.12.2004р. Про затвердження протоколів надання медичної допомоги за спеціальністю «Нефрологія». «Протокол надання медичної допомоги хворим з артеріальною гіпертензією при ураженні нирок».
8. Наказ МОЗ та АМН України за № 43/454 від 10.07.2006р. «Про затвердження форми медичної облікової документації, форми звітності та інструкцій щодо їхнього заповнення з питань реєстрації пацієнтів з хронічною хворобою нирок (ХХН)».
9. Deferri G, Ravera M, Berruti V, Leoncini G, Deferrari L, optimizing therapy in the diabetic patient with renal disease antigipertensive treatment. //J AM soc Nephrol -2004. –N-15 (suppl 1).-P. 6-11
10. Dominguez L.J., Barbagello M., Kattah W. et la quinaptil reduces microalbuminuria in essential Hypertension and in diabetic hypertensive subjects // Am. J. Hypert -1995.-N-8- P. 808-814
11. Heeg JE, De Jong PE, VanDerHem GK, DE Zeeuw D: reduction of proteinuria by angiotensin converting enzyme.// Kidney Int-2000.-N-32-P.78-83
12. Levey AS. Adler S, Caggiula AW, England BK, Greene T, Hunsicer LG, Kusek JW, Rogers NL, Teschan PE, short-term effects of protein intake, blood pressure, and antihyoertensive therapy on glomerular filtration rate in the modification of diet in renal disease study // J Am Nephrol -2002.-N-7-P. 2097-210
13. «Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy». The GISEN Group (Gruppo Italiano di Studi Epidemologici in Nefrologia). Lancet 1997;349:1857—63.
14. Rossing K, Christensen PK, Hoving P, Tarnow L, Rossin P, Parving HH, Progression of nephropathy in type 2 diabetic patients. // Kidney Int-2000.-N-66-P.1596-1605
15. Siragy HM. AT1 and AT2 receptor in the kidney: role in health and disease. //Simin Nephrol.-2004.- N-24 – P.93-100
16. Strippoli GFM, Craid M, Deeks JJ, Scheena FP, Craing JC, Effects of angiotensin converting enzyme inhibitors and angiotensin II receptotor antagonists on mortality and renal outcomes in diabetic nephropathy: systemic review //BMJ-2004.-N-329.-P.828-838
17. Taal MW, Brenner BM Reno protection of RAS inhibition: from ACEI to angiotensin II antagonists.//Kidney Int.-2000-N-57-P.1803-1817