ANTIHYPERTENSIVE THERAPY IN COMORBID PATIENTS WITH CHRONIC KIDNEY DISEASE: A CLINICAL OBSERVATION

Tursunova M.A.

Assistant of the Department of Propaedeutics of Internal Diseases

Andijan State Medical Institute

Andijan, Uzbekistan

Abstract

Arterial hypertension (AH) is a global health problem and one of the leading risk factors for the development of cardiovascular diseases (CVD) and chronic kidney disease (CKD). Hypertension occurs in 30-45% of the adult population and can be both a cause and a consequence of CKD.

The pathophysiology of hypertension associated with CKD includes various mechanisms of increased blood pressure (BP), including changes in the activity of the renin-angiotensin-aldosterone system. The comorbidity of hypertension and CKD increases the risk of developing end-stage chronic renal failure, cardiovascular and cerebrovascular complications. Controlling blood pressure in patients with CKD helps reduce this risk and slow the progression of kidney disease.

According to коморбидныхcurrent clinical guidelines for hypertension, a combination of antihypertensive drugs (AHPs) should be considered as a starting drug therapy in comorbid patients with hypertension and CKD антигипертензивныхto achieve the target blood pressure level. Additional renoprotective and/or cardioprotective effects should be considered when choosing medicationскардиопротективное. The results showed that the combination of angiotensin converting enzyme (ACE) inhibitors and блокаторовcalcium channel blockers (CCB) is most optimal for the treatment of patients with hypertension and CKD. According to the current strategy of combination therapy, the appointment of fixed combinations (FC) of AHP is most preferable. This paper presents a clinical observation of the successful use of ACE inhibitor FC/BCC in a comorbid patient with hypertension and CKD.

Keywords: arterial hypertension, chronic kidney disease, clinical observation, ramipril, amlodipine.

Introduction

The prevalence of arterial hypertension (AH) in general in the adultpopulation is3-6-48–48%, and amongelderlypeople it reaches 6.2% [1]. The disease is diagnosedin 4.1% of women and4.6% of men [2]. Hypertension contributes to the development of cardiovascular diseases(CVD), increases the risk of mortality and disability by 70% [1]. According to the NHANES (National Health and Nutrition Examination Survey) registry, 20% of patients with hypertension Nutrition Examination Surveyare diagnosed with chronic kidney disease (CKD) with varying degrees of renal dysfunction [3, 4]. CKD, in turn, occurs in 10-15% of the world's population, ranking 16th. place among the causes of loss of

years of life [5]. CKD is manifested by renal dysfunction (estimated glomerular filtration rate (eGFR) <60 ml / min/1.73m2 [3]) or signs of renal damage (albuminuria, changes in urine sediment, metabolic or structural disorders) for 3 months or more. The progression of CKD is indicated by a decrease in eGFR by 25% or more from baseline or a decrease in eGFR by more than 5 ml/min/1.73m2 per year [6, 7].

Depending on the degree of eGFR reduction, there are 5 stages of CKD. The staging also takes into account the level of albuminuria. In addition, due to the peculiarities of the prognosis for patients, stages 3a and 3b are distinguished (eGFR 45-59 ml / min/1.73m2 and 30-44 ml / min/1.73 m2, respectively) [6]. For patients with stage 3b (eGFR 30-59 ml / min/1.73m2) or stage 4 (eGFR 15-29 ml / min/1.73 m2) CKD, the risk of death from CVD was higher than the risk of progression to end-stage chronic renal failure (ESRD) (eGFR<15 ml / min/1.73 m2) [8]. In the case of comorbidity of CKD and hypertension, the risk of developing CVD complications increases [9].

Comorbidity of hypertension and CKD

The prevalence of hypertension among patients with CKD reaches 90%, and as eGFR decreases, the frequency and severity of the disease increases [10]. Other CVD conditions are also common among people with CKD. It was shown that among 175,840 adults with CKD aged 66 years and older, concomitant CVD was diagnosed in 65%, while among 1 086 232 adults without CKD-only in 32% [10]. Moreover, CKD is associated with worse cardiovascular outcomes. A study [10] demonstrated that the presence of CKD worsened two-year survival rates in patients with CVD .

Pathogenetic mechanisms коморбидностиof HYPERTENSION and CKD comorbidity

Pathogenetic mechanisms such as activation of the renin-angiotensin-aldosterone system (RAAS), salt and water retention, endothelial dysfunction, and increased arterial vessel wall stiffness [11-13] lead to the development of persistent hypertension and CKD progression due to the development of hypertensive nephroangiosclerosis [14] and contribute to the comorbidity of these diseases.

A significant factor in the progression of CKD is protein uria (PU), which occurs when the kidneys are damaged. Subsequently, PU, becoming an autonomous factor, contributes to the progression of renal pathology, the development of CVD and their complications [15]. Quantification of PU allows you to stratify this risk, and can also be used to assess the response to treatment. "Gold standard" — determination of the daily PU. In practical medicine, the determination of the ratio of albumin to creatinine in morning urine (ACR)is more often used as the equivalent of determining the daily PU, the ACR value≥3 mg /mmol is sufficient for the diagnosis of CKD regardless of eGFR [16].

Principles of drug therapy in comorbid patients

According to epidemiological data, from 30 to 60% of patients with hypertension do not achieve stable blood pressure stabilization at the target level, which is especially important for high-risk patients [17].

Achieving the target BP values in patients with hypertension and CKD leads to a decrease in PU, a slowdown in the rate of eGFR decline, a decrease in the frequency of CVD and the risk of ESRD, which generally improves the prognosis [18].

Current clinical guidelines for AH[1] recommend that systolic blood pressure (SBP) 130-139 mm Hg. ст., and diastolic blood pressure (DBP) 70-79 mm Hg as the target BP level in adults with CKDрт.

The CKD[2 clinical guidelines]for high-risk patients with CKD and PU (PU≥500 mg/day or ACR≥500 mg/g) recommend нефропротективнойreducing SBP to 120-130 mm Hgand DBP < 80 mm Hg for nephroprotective purposes and in the absence of contraindicationsрт.

Lowering blood pressure to lower values (target SBP<120 mm Hg), according to the new KDIGO (Kidney Disease Improving Global Outcomes) guidelines [19], can provide higher renoprotection in individuals with significant PU (>1 g /day or ACR>70 mg / g). Based on the results of the Systolic Blood Pressure Intervention (SPRINT) study [20], achieving SBP <120 mm Hg(compared to SBP <140 mm Hg) is associated with a 25% reduction in the risk of cardiovascular complications and 27% reduction in all-cause mortality [20]. However, it should be noted that a pronounced decrease in blood pressure can negatively affect the state of renal blood flow with the development of ischemic kidney damage1.

When choosing drug therapy, it should be remembered that some AHPs, in addition to direct BP reduction, provide additional independent renoprotective and / or cardioprotective effects [21].

An important factor in the treatment of hypertension in CKD is the effect of the drug on PU. In particular, the blockade of RAAS provides a BP-independent reduction in PU [22]. Accordingly, AHPs блокаторовof the RAAS blocker class (ACE inhibitors (aCEI) andблокаторыangiotensin II receptor antagonists (blockers)ангио-тензина) have the properties of both cardioprotectorsand nephroprotectors and therefore are of particular value for the treatment of patients with CKD, being first-line drugs. БлокаторыRAAS blockers provide a BP-independent reduction in PU in both diabeticand nondiabetic CKD [22]. It should be noted that timely administration блокаторовof RAAS blockers reduces the possibility of microalbuminuria [23].

To achieve the target BP values in patients with CKD, combination drug therapy is recommended1. 1 In 2008, data from the COMPLETE study (Avoiding Cardiovascular Events in Combination therapy in Patients Living with Systolic Hypertension) were presented, which focused on the prevention of cardiovascular events through combination therapy in patients with hypertension. This study was the first to evaluate the effectiveness of combined dihydropyridine BCC and ACE

inhibitors in reducing CVD mortalitycompared with a combination of a thiazide diuretic (TD) and ACE inhibitorsin patients with hypertension and a high risk of CVD associated with diabetes mellitus (DM), left ventricular hypertrophy, peripheral artery disease, CKD, or a history of CVD [24]. The COMPLETE trial was terminated prematurely due to the higher efficacy of the ACE inhibitor/ACE inhibitor combination for CVD mortality, which confirmed the synergistic properties блокатораof the RAAS blocker and ACE inhibitor in cardioprotection. The use of a fixed combination (FC) of ACE inhibitors/amlodipine reduced the risk of cardiovascular death by 38% compared to the FC of ACE inhibitors/hydrochlorothiazide. It is noteworthy that the rate of progression of kidney pathology was also lower by 48% in the amlodipine BCC group, regardless of the achieved BP values. These results suggest that the addition of BCC amlodipine to ACE inhibitor therapy actually has an additional nephroprotective effect compared to the addition of TD in this risk group [24].

Clinical observation

Patient K.,6-4 years old, complained of constrictive headaches; non-systemic dizziness; blood pressure rise to the level of 165/90-95 mm Hg, frequent, painless urination, nocturia..

Medical history

The above complaints bothered the patient for 6 years, she was not examined for this reason, occasionally took amlodipine 5 mg on her own, and the drug was well tolerated. During the last year, the state of health has worsened: headaches have become more frequent, with a predominant localization in the parietal-occipital region; frequent urination has appeared at night (2-3 times a night), which has led to sleep disorders and poor health during the day. The patient began to notice a significant increase in blood pressure: SBP up to 160-165 mm Hg, DBP up to 90-95 mm Hg. The deterioration of the condition is associated with non-compliance with the diet, weight gain of 10 kg and lack of treatment.

Denies bad habits. From the transferred diseases, he notes frequent acute respiratory infections. He denies any injuries or operations. The allergic history is not burdened. Heredity is burdened by CVD: the father died of a myocardial infarction at the age of 70. The patient is unemployed, retired, and lives in rural areas.

Objective inspection data

The patient is overweight: BMI 29.7 kg /m2, waist circumference9.4 cm; skin and visible mucous membranes of normal color, no lymphadenopathy and peripheral edema, focal neurological symptoms were not detected. Assessment of the state of the cardiovascular system: during percussion — the left border of relative dullness of the heart is 0.5 cm inside from the left mid-clavicular line;

during auscultation, the rhythm is correct, the heart tones are muted, the emphasis of the second tone is on the aorta. Heart rate7-8 in 1 min, blood pressure 165/95 mm Hg.

The patient was examined by an ophthalmologist. An increase in arteriole tone with narrowing of their lumen (a "wire" symptom) was found, venular tone was reduced, and the vessels were convoluted.

Laboratory tests

Indicators of the general blood test within the reference values.

In the biochemical analysis of blood, the laboratory picture of impaired lipid metabolism and nitrogen-releasing function of the kidneys: total cholesterol 6.6 mmol/l (norm 3.1–6.2 mmol/L); HDL cholesterol 1.37 mmol/l (norm 0.9–2.0 mmol/L); LDL cholesterol 5.99 mmol/l (norm 2.28-5.26 mmol/L); triglycerides 1.75 mmol/ l (norm <2.3 mmol/L), atherogenicity index 3.3 (norm <3); creatinine 115 mmol/l (norm 55-105 mmol/L), urea 7.3 mmol/l (norm 2.8-8.0 mmol/L).

In the general analysis of urine-a laboratory picture of a decrease in the concentration function of the kidneys (hypostenuria, relative density 1013), an alkaline reaction of urine (pH 6.0).

In the Zimnitsky urine test, a laboratory picture of hypostenuria, nocturia, indicating tubulopathy (relative urine density 1008-1015, daytime diuresis 500.0 ml, nocturnal diuresis 800.0 ml).

In the Rehberg sample, glomerular filtration rate decreased to 59 ml/min, and tubular reabsorption decreased to 98%, which indicates damage to the renal glomeruli and tubules. eGFRcalculated using the CKD-EPI formula was 60 ml / min/1.73m2.

Attention was drawn to the laboratory picture of hyperalbuminuria as an early marker of renal damage and an independent risk factor for CVD and its complications. Daily urinary albumin excretion was 84 mg /day (norm 0-29 mg /day), the ratio of albumin to creatinine (in the morning portion of urine) was 6.5 mg/mmol (norm <3 mg/mmol).

Data from instrumental research methods

Electrocardiography data: sinus rhythm, deviation of the electrical axis of the heart to the left, signs of left ventricular myocardialhypertrophy. The Sokolov — Lyon index 3is 3.6 mm.

Данные Echocardiography data: a slight increase in the size of the left atrial cavity. Left ventricular myocardial hypertrophy. No areas of local myocardial contractility were detected. Global myocardial contractility is not affected. The emission fraction is 64%. Violation of the diastolic function of the left ventricle in the first type. There were no signs of pulmonary hypertension.

With daily мониторированиимonitoring of blood pressure (ABPM), periods of its increase were recorded during the day. The maximum increase in blood pressure to 165/98mm HgDuring daytime hours wed the currentSBP value was8 рт15.8 mm Hg, DBP-9.6 mm Hg; at night: SBP13.7 mm Hg, DBP 87 mm HgIncreased variability of SBP and DBP was noted, and the diurnal BP profile was non-dipper.

Данные Daily ECG monitoring data: the main rhythm is sinus. The average heart rate during the day is 73 in 1 min, at night-60 in 1 min, the average value per day is 69 in 1 min. Maximum heart rate-128 in 1 min; minimum heart rate-51 in 1 min. No rhythm pauses lasting more than 2 seconds were registered. No episodes of significant ST segment displacement were recorded.

Ultrasound examination of the kidneys and adrenal glands revealed echographic signs of diffuse changes in the renal parenchyma, a decrease in speed indicators and a violation of renal blood flow in the interlobar parts of the renal artery of both kidneys. The revealed changes in the kidneys with a violation of their blood supply can be accompanied not only by renal dysfunction, but also by an aggravation of the course of hypertension.

When assessing the condition of the main vessels, taking into account lipid metabolism disorders and age, according to ultrasound Dopplerography of the bracheocephalic arteries, a flat atherosclerotic plaque with a thickness of 2.2 mm and a length of 4.7 mm, with clear even contours, was found in the area of the bifurcation of the common left carotid artery (CCA), stenosing CCA by 27%.

Based on complaints, examination data and additional research methods, the diagnosis was established: hypertension of stage II, 2nd degree, risk 3 (high); hyperlipidemia, left ventricular myocardial hypertrophy. CKD stageC2, GFR (according to the CKD-EPI formula) 60 ml / min/1.73 m2, grade A2 (according to the KDIGO classification). Target blood pressure is 130-139 / 70-79 mmHg.

The patient is recommended a diet with restriction of animal fats, easily digestible carbohydrates, purine-rich foods, salt up to 5 g /day, a physical activity regime (30 minutes of moderate-intensity physical activity 5 days a week (walking, Nordic walking)).

Taking into account the comorbid pathology (combination of hypertension and CKD), the patient was prescribed treatment with FC AHP amlodipine 5 mg and ramipril 10 mg (Egipres®, EGIS, Hungary) 1 r/day in the morning. Taking into account the high risk on the SCORE scale (6%), rosuvastatin 10 mg was prescribed in the evening.

By the end of the 1st week of treatment, a positive trend was noted in the form of regression of pain syndrome, a decrease in the severity of hypertension (maximum SBP of 150 mm Hg, maximum DBP of 90 mm Hg). While taking Egipres® for a monthбыл, the target blood pressure level of 130/75–80 mm Hg was achieved. In the future, the target blood pressure level was maintained (according to self-monitoring and office blood pressure measurement). The patient noted good tolerability of the treatment.

When monitoring laboratory parameters after 3 months, a positive trend was noted: the level of total cholesterol decreased to 5.5 mmol/l, LDL cholesterol to 3.99 mmol/l, triglycerides to 1.65 mmol/l, and the atherogenicity index to 2.9.

Indicators of the functional state of the kidneys also showed positive dynamics. The results of the Zimnitsky urine test indicated an improvement in the concentration function of the kidneys: the relative density of urine was 1012-1018, nocturia passed. There was an improvement in filtration (eGFRcalculated by the CKD-EPI formula was 66 ml/min/1.73m2) and nitrogen-releasing renal function (creatinine 103 mmol/ l). Normoalbuminuria was detected in the assessment of daily albumin excretion and determination of the ratio of albumin to creatinine inвыявленathe morning urineнормоальбуминурия.

According to the results of repeated ABM, there was a decrease in the average daily SBP by 26 mm Hg, the average daily SBP by 21 mm Hg, the average daily DBP by 16 mm Hg, and the average daily DBP by 19 mm Hg. The variability of SBP and DBP in daytime and night hours returned to the normal range.

When examined after 5 months, against the background of continuous administration ofEgipres®, the patient has a persistently normal blood pressure level (normotension), and she feels satisfactory. During ultrasound of the kidneys, an improvement in renal blood flow parameters was noted in dynamics.

Thus, antihypertensive therapy with FC amlodipine 5 mg and ramipril 10 mg (Egipres® 5/10) contributed to achieving the target blood pressure level by the 4th week of treatment with stable blood pressure control in the future. Along with a high antihypertensive effect, we observed a pronounced nephroprotective effect, confirmed by the positive dynamics of laboratory parameters of filtration, concentration, and nitrogen-releasing renal function and the regression of albuminuria to normal by the 3rd month of treatment with Egipres®, which, of course, improved the quality and prognosis of the patient's life. That is why the patient was recommended to continue treatment with FC amlodipine/ramipril in the same mode.

Discussion

Based on current clinical guidelines for the treatment of hypertension, the initial therapy of comorbid patients with hypertension and CKD involves the appointment of a combination блокатораof an RAAS blocker with BCC. Among the representatives of the ACE inhibitor class препаратом выбора служит , ramipril is the drug of choice, which is characterized by a rapid onset of antihypertensive effect (after 1-2 hours). The long half-life of ramipril (from 8 to 14 hours) determines the effective control of blood pressure during the day, which is confirmed by the results of the PRISMA I (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) study [25]. The peculiarity of the therapeutic effect of this drug is that with a pronounced decrease in total peripheral resistance, renal blood flow does not suffer, and the absence of a sulfhydryl group in the structure excludes its nephrotoxicity. Due to its high lipophilicity , ramipril has a pronounced organoprotective effect [26]. The MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal

Outcomes in the Heart Outcomes Prevention Evaluation) sub-study [27] in the largeHeart Outcomes Prevention EvaluationHeart Outcomes Prevention Evaluation study, which included 3,577 patients with DM with an average age of 65.4 years, showed that ramipril significantly reduced the relative risks of cardiovascular mortality by 25% and the relative risk of death from all causes by 24%. The frequency of microalbuminuria in the ramipril group was also significantly lower, which reduced the risk of PU and proved a high nephroprotective efficacy of the drug in patients with DM, especially in the initial microalbuminuria. The results of the clinical study REIN (Ramipril Efficacy in Nephropathy) in patients with chronic nondiabetic nephropathy (with PU>1 g/day) demonstrated a significant nephroprotective effect. It should be noted that the nephroprotective effect was more pronounced in patients with significant PU. рамиприлаESRD was 58% lower in the ramipril group than in the placebo group. With further follow-up of these patients for three years, the level of PU decreased by another 13% in the ramipril group (p=0.003), while in the placebo group it increased by 15%, and in the same group 30% of patients developed chronic renal failure [28].

Conclusion

The comorbidity of hypertension and CKD determines a high risk of developing cardiovascular and renal complications. According to current clinical guidelines, FC AHP is recommended as a starting therapy for high-risk patients to achieve the target blood pressure level and improve the prognosis. First-line medications are блокаторыRAAS blockers. ACE inhibitor ramipril has been shown to have high antihypertensive and organoprotective (including nephroprotective) effects, which makes it the drug of choice in patients with hypertension and CKD. When prescribing combination therapy, taking into account the evidence base, the use of dihydropyridine BCC is indicated as the second drug. FC блокатораof the RAAS blocker and BCC (ramipril/amlodipine) promotes effective blood pressure control at the target level and provides organoprotective action, improving the quality of life and prognosis of a comorbid patient. FC reduces the risks of polypharmacy and improves drug safety.

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