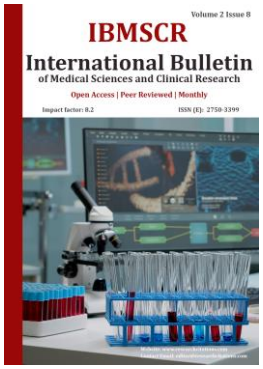

OPTIMIZATION OF THERAPY FOR CARDIORENAL SYNDROME IN PATIENTS WITH CHRONIC HEART FAILURE.

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Abstract: Chronic heart failure (CHF) in the XXI century is very important as a medical, economic and social problem. Acute decompensation of CHF (ADCHF) is a common cause of hospitalization and mortality in patients with CHF. The article presents an analysis of the incidence, prognostic value, features of the occurrence of renal failure in patients with ADHF, as well as the effect of drugs from the group of angiotensin receptors and neprilysin inhibitor - ARNI (valsartan / sacubutril) used in the treatment of ADHHF, on renal function, the features of their use in conditions of deterioration of the functional state of the kidneys.

Key words: cardiorenal syndrome, chronic heart failure, drugs from the ARNI group.

Chronic heart failure (CHF) is a syndrome that occurs as a result of a violation of the ability of the heart to fill and / or empty, taking place in conditions of an imbalance in the vasoconstrictor and vasodilating neurohormonal systems and accompanied by insufficient perfusion of organs and tissues of the body. Acute decompensated heart failure (ADHF) is a period of CHF, which is manifested by a rapid worsening of symptoms of heart failure (HF), requiring emergency hospitalization of the patient for intensive care.

Most often, patients with ADHF are concerned about severe shortness of breath, which occurs due to stagnation of fluid in the lungs, which is one of the main manifestations of this condition. Therefore, elimination of excess fluid should be the primary goal of treatment. In addition, there is strong evidence that fluid retention in the lungs worsens the prognosis of the disease. The kidney is the main organ for fluid excretion, but many patients with acute HF (AHF) have initial renal dysfunction in the form of decreased glomerular filtration rate (GFR) or worsen kidney function on admission.

Given the close relationship between the work of the kidneys and the heart, described back in 1836 by R. Bright, a violation of cardiac function can cause renal dysfunction, which was designated as cardiorenal syndrome (CRS). In 2008, C. Ronko et al. classified cattle into 5 types.

Type 1. Acute CRS: Abrupt decline in cardiac function leading to acute renal failure (ARF). Causes: acute heart failure (AHF), cardiac surgery, acute coronary syndrome (ACS), contrast-induced nephropathy after coronary angiography .

Type 2 Chronic CRS: Chronic cardiac dysfunction leading to chronic renal failure (CRF). Causes: ischemic heart disease, arterial hypertension, congenital heart disease, chronic heart failure (CHF) .

Type 3. Acute renocardial syndrome: Abrupt decline in renal function leading to the development of AHF. Causes: acute pulmonary edema in acute renal failure, arrhythmias, contrast-induced nephropathy leading to cardiac dysfunction.

Type 4 Chronic Renocardial Syndrome: CRF leading to chronic cardiac dysfunction. Causes: left ventricular myocardial hypertrophy in CRF, cardiovascular dysfunction in CRF, autosomal dominant polycystic kidney disease.

Type 5. Secondary cardiorenal syndrome: Other comorbid conditions leading to the development of cardiac and renal dysfunction. Causes: sepsis, diabetes mellitus, systemic lupus erythematosus, sarcoidosis, amyloidosis.

CRS is present in 32–90.3% of patients with HF. An important link in the pathogenesis of the formation of impaired renal function in CHF was a change in the activity of neuroendocrine mechanisms. Activation of the renin-angiotensin-aldosterone (RAAS) and sympathoadrenal systems led to vasoconstriction in the kidneys, a decrease in the volume of blood flow in them, the development of chronic ischemia with a decrease in the functional abilities of the renal glomeruli. Hemodynamic shifts and activation of neuroendocrine mechanisms provoked the development of subclinical inflammation of the kidneys. This was accompanied by an increase in inflammatory markers such as lipopolysaccharide-binding protein, interleukins, and the number of activated monocytes.

An important role is played by endothelial dysfunction, which develops as a result of a high level of markers of inflammation and oxidative stress in patients with CHF in the development of type 2 CRS. Cross damage to the heart and kidneys was accompanied by excessive expression of cytokines and chemokines, increased migration of neutrophils, which caused the progression of endothelial dysfunction and induced long-term organ dysfunction, cardiac death. Early diagnosis of CRS allows timely start of treatment, prevention of complications and reduction of mortality. Currently, great importance is given to the determination of biomarkers of the disease.

The biomarker should be detected in the early stages of the disease, indicate the time and severity of the damage, have high sensitivity, specificity, and allow predicting the course of the disease. A biomarker that is detected in the early stages of AKI is neutrophil gelatinase-associated lipocalin (NGAL), which precedes the increase in creatinine by 48-72 hours. In accordance with the data presented by R. G. VandeVoorle (2006), cystatin C correlates with the duration and severity of AKI, the need for patients in renal replacement therapy (RRT) and hospital mortality.

Kidney injury molecule (KIM-1) is a protein that is found in the urine after ischemic or toxic damage to the proximal tubules. KIM-1 is an important and highly sensitive biomarker for the early stages of AKI. In addition to the biomarkers listed above, in scientific publications one can find mention of interleukin-18, the lysosomal enzyme N-acetyl-β-d-glucosaminidase, which allow the diagnosis of AKI. As for the diagnosis of acute myocardial injury, it is necessary to note NUP, which is found in acute heart failure or decompensation of CHF.

Troponin is a recognized marker of myocardial necrosis. An increase in troponin levels is associated with an increase in mortality in CKD and has a prognostic value for type 4 cattle. Current markers of CKD progression are microalbuminuria, proteinuria, C-reactive protein levels, and decreased GFR. Serum creatinine is a simple but important indicator to determine the survival of patients with CHF. According to the results presented by G. I. Smith et al. (2003) an increase in serum creatinine concentration during hospitalization by 0.2 mg / dl or more increases the risk of death over the next 6 months by 67% and the likelihood of readmission by 33%.

CRS is a global health burden for patients. Angiotensin-converting enzyme inhibitors, β-blockers, mineralocorticoid receptor antagonists and diuretics have consistently remained the main drugs for the treatment of patients with CHF for many years. Signs and symptoms of volume overload were the most common cause of hospitalization for ADHF. Loop diuretics in this case were the only effective pharmacological agent. Therefore, they were the main method of treatment in patients with stable hemodynamics.

Diuretic therapy for acute conditions remained largely empiric. The effectiveness of diuretics often decreased with the progression of heart failure, incl. with ODHS. This required an increase in their dose or the use of an alternative in the form of extracorporeal ultrafiltration. Inhibition of the neurohumoral axis and adequate treatment of hypervolemia are fundamental elements of modern heart failure therapy. This direction has opened up new opportunities for realizing the potential benefits in reducing cardio-renal adverse outcomes in patients with CHF and CKD comorbidity.

If a situation arises when, despite the action of complex therapy consisting of a RAAS blocker (ACE inhibitor / ARA II), BAB, diuretic, clinical symptoms of CHF persist (shortness of breath, swelling, weakness, fatigue, palpitations), it is necessary to replace the ACE inhibitor / ARA II with ARNI .(angiotensin receptor neprilysin inhibitor). Neprilysin is a neutral endopeptidase that cleaves peptides, mainly natriuretic bradykinin, increasing the level of natriuretic peptides. Mechanism of action: The two active substances, sacubitril and valsartan, work differently.

Valsartan blocks the action of a kidney hormone (angiotensin II), which can be harmful to patients with heart failure, by blocking the receptors to which angiotensin II normally attaches. This allows you to stop the harmful effects of the hormone on the heart and provide the blood vessels with the opportunity to expand. Sacubitril blocks the breakdown of natriuretic peptides produced in the body. Natriuretic peptides cause the conversion of sodium and water into urine. This effect reduces the workload on the heart and blood pressure. The combined effect of the two drugs reduces the workload on the heart in heart failure.

Its use increases diuresis, natriuresis, improves myocardial relaxation, reduces the release of renin and aldosterone. To date, ARNI includes one drug, which is a cross-linked molecule of valsartan (APA II) and sacubitril (a neprilysin inhibitor). ARNI is recommended for use in patients with chronic heart failure with reduced EF of a stable course (without decompensation, intravenous administration or doubling the dose of oral diuretics and with systolic blood pressure > 100 mm Hg), with tolerance to ACE inhibitors (or ARA II).

Transfer of this category of patients to ARNI (at a starting dose of 100 (49/51) mg × 2 times a day not earlier than 36 hours after the last dose of ACE inhibitors (ARA), followed by dose titration to the optimal 200 (97/103) mg × 2 times a day is given to further reduce the risk of death and subsequent hospitalizations for CHF.19 In the US, a randomized clinical trial was conducted among 881 patients with heart failure with reduced ejection fraction, hospitalized for ADHHF.The patients were divided into groups (440 and 441 people) who were randomly assigned to receive sacubitril-valsartan (target dose, sacubitril 97 mg with valsartan 103 mg twice daily) or enalapril (target dose, 10 mg twice daily), respectively.

Based on these data, among HF patients with reduced ejection fraction hospitalized for ADHHF, initiation of sacubitril-valsartan therapy resulted in a much greater decrease in the concentration of brain natriuretic peptide (NT-proBNP) than enalapril therapy. At the same

time, the incidence of deterioration in renal function, hyperkalemia, symptomatic hypotension and angioedema did not significantly differ between the two groups, from which it can be concluded that the use of ARNI is most appropriate for patients with ADHHF in comparison with enalapril, as well as in general in terms of the treatment of CHF.

Also in the United States, a study was conducted in which it was found that patients receiving sacubitril-valsartan needed lower doses of loop diuretics than patients taking enalapril along with loop diuretics to achieve adequate diuresis.

Conclusion: Based on the analyzed data, the treatment of ADHF requires a thorough analysis of the patient's clinical condition with the determination of kidney function, as well as dynamic monitoring to achieve stable compensation for the manifestations of stagnation, subsequent monitoring at the outpatient stage, which will reduce the number of readmissions and deaths. Currently, changes in kidney function in patients with ADHHF and the factors influencing this process remain not fully understood, which requires further research.

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