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ПЕРСОНАЛИЗИРОВАННАЯ ФАРМАКОЛОГИЧЕСКАЯ КОРРЕКЦИЯ ИММУННЫХ, МЕТАБОЛИЧЕСКИХ И НЕЙРОПСИХИЧЕСКИХ ПАРАМЕТРОВ ПРИ ХРОНИЧЕСКОЙ ИШЕМИИ МОЗГА I И II СТАДИИ НА ФОНЕ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ

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Резюме. Целью исследования была разработка персонализированной фармакологической коррекции иммунных, метаболических и нейропсихических нарушений при хронической ишемии мозга (ХИМ) I и II стадии. В исследование было включено 104 пациента, из которых 76 больных женского и 28 мужского пола, с ХИМ на фоне гипертонической болезни II степени, из которых 52 больных были с I стадией и 52 со II стадией в возрасте 50±5 лет. Изучены клинические и лабораторные показатели у 22 здоровых доноров того же возраста, сформировавших контрольную группу. Рандомизация больных с ХИМ проводилась по полу, возрасту, способу лечения, сопутствующей патологии, длительности заболевания. Оценку клинико-лабораторных данных осуществляли в начале лечения и через 2 недели после его окончания. Определяли в плазме крови и эритроцитах сорбционную способность эритроцитов и сорбционную емкость гликокаликса (СЕГ), активность процессов перекисного окисления липидов, состояние антиоксидантной системы, выявляли уровень стабильных метаболитов оксида азота (SMNO), неоптерина, С-реактивного белка, цитокинов (TNFα, IL-1β, IL-8, IFNγ, IL-18, G-CSF, IL-4, IL-10), иммуноглобулинов (IgM, IgG, IgA), компонентов системы комплемента (C3, C4, C5, C5A), фагоцитарную и кислородзависимую активность полиморфноядерных лейкоцитов крови. Установлено, что пациентам с ХИМ I с высокими значениями концентрации IL-8, IL-10, SMNO и низким показателем СЕГ, прием церетона и актовегина или цераксона и мексикора будет недостаточен для эффективной коррекции иммунометаболических нарушений, что требует дополнительного назначения иммуномодулятора. Пациентам с ХИМ II, имеющим более высокий уровень в плазме TNFα, IL-10 и низкие значения СЕГ, необходимо назначение цераксона, мексикора и глутоксима или цераксона, мексикора и полиоксидония с целью получения максимального клинико-лабораторного положительного эффекта.

Ключевые слова: хроническая ишемия мозга, персонализированная фармакологическая коррекция иммунометаболических нарушений

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PERSONALIZED PHARMACOLOGICAL CORRECTION OF IMMUNE SYSTEMS, METABOLIC AND NEUROPSYCHIC PARAMETERS IN CHRONIC BRAIN ISCHEMIA OF STAGE I AND II ON THE BACKGROUND OF HYPERTENSION DISEASE

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Abstract. The study aimed to develop a personalized pharmacological correction of immune, metabolic and neuropsychiatric disorders in chronic cerebral ischemia (CCI) stages I and II. The study included 104 patients, of which 76 were female and 28 were male, with CCI on the background of grade II hypertension, of which 52 patients were with stage I and 52 with stage II at the age of 50±5 years. Clinical and laboratory parameters were studied in 22 healthy donors of the same age who formed a control group. Patients with CCI were randomized according to gender, age, treatment method, concomitant pathology, and duration of the disease. Evaluation of clinical and laboratory data was carried out at the beginning of treatment and 2 weeks after its end. The sorption capacity of erythrocytes and the sorption capacity of the glycocalyx (SEG), the activity of lipid peroxidation processes, the state of the antioxidant system were determined in blood plasma and erythrocytes, the level of stable metabolites of nitric oxide (SMNO), neopterin, C-reactive protein, cytokines (TNFα, IL-1β, IL-8, IFNγ, IL-18, G-CSF, IL-4, IL-10), immunoglobulins (IgM, IgG, IgA), complement system components (C3, C4, C5, C5A), phagocytic and oxygen-dependent activity of polymorphonuclear blood leukocytes. It has been established that for patients with CCI I with high concentrations of IL-8, IL-10, SMNO and a low SEG index, the intake of Cereton and Actovegin or Ceraxon and Mexicor will be insufficient for effective correction of immunometabolic disorders, which requires additional administration of an immunomodulator. Patients with CCI II, who have a higher plasma level of TNFα, IL-10 and low SEG values, need to prescribe Ceraxon, Mexicor and Glutoxim or Ceraxon, Mexicor and Polyoxidonium in order to obtain the maximum clinical and laboratory positive effect.

Keywords: chronic cerebral ischemia, personalized pharmacological correction of immunometabolic disorders

Introduction

Today, personalized or precision medicine is a new doctrine of modern health care, which is based on the use of new methods of molecular analysis (genomics, transcriptonics, proteomics, metabolomics, microbiomics) to improve the assessment of predisposition (prediction) to diseases and their "management" (prevention and treatment).

Personalized medicine takes into account the individual's genetic program, clinical, demographic, laboratory, and instrumental predictors of response to therapy and the risks of possible complications, includes analysis of drug metabolism, immune response, which significantly affect the specifics of the body's response to a particular drug, as well as monitoring treatment using biomarkers. This allows to make medical treatment as effective and safe as possible for a specific patient. Thus, personalized medicine can be considered as an innovative and intensive tool for modernizing the healthcare system and improving the quality of life of patients [1, 2, 5, 8].

Materials and methods

The investigstion included 104 patients, including 76 female and 28 male patients, who made up the main group of hospitalized in the neurological Department of Kursk regional clinical hospital, with correction of blood pressure to the normal level, with CHEB against the background of grade II hypertension, of which 52 patients were stage I (1st main group) and 52 with stage II (2nd main group) at the age of 50±5 years.

In addition, clinical and laboratory parameters were studied in 22 healthy donors (52±2 years) who formed the control group 1; the results were accepted as normal.

Randomization of patients with CHEB was performed by gender, age, method of treatment, accompanied pathology, and duration of the disease.

The criteria for inclusion in the main group were: age from 40 to 60 years; the absence of accompanied diseases in the acute stage, the presence of CHEB against the background of grade II, stage II hypertension, risk 2, diagnosed 5 or more years ago in accordance with the recommendations of the world health organization and the International society on arterial hypertension (MOG, 1999).

The exclusion criteria were: symptomatic arterial hypertension; severe or moderate atherosclerotic changes in the fundus vessels; heart rhythm and conduction disorders; chronic heart failure of more than II FC in accordance with the classification of the new York heart Association (NYHA); hemodynamically significant stenoses of brachiocephalic and cerebral vessels, heart defects; myocardial infarction, postinfarction cardiosclerosis and progressive angina or indications thereof a history of diabetes or impaired glucose tolerance.

For all the patients underwent a comprehensive clinical and instrumental examination according to generally accepted standards, and in all cases, the diagnosis of stage I and II CHEB was verified. The treatment followed the principles of evidence-based medicine.

Evaluation of clinical and laboratory data in the main groups was performed at the beginning of treatment and 2 weeks after its end. From 10 ml of heparinized blood, plasma and red blood cell mass were obtained by centrifugation, with which the sorption capacity of red blood cells (SSE) and the sorption capacity of glycocalyx (SEG) were immediately determined.

The intensity of lipid peroxidation processes was assessed by the content of acyl hydroperoxides and malondialdehyde (MDA and AGP) in blood plasma and erythrocytes.

The conduction of the antioxidant system was determined by direct/competitive solid-phase enzyme immunoassay using ready-made commercial kits : the activity of superoxide dismutase (SOD) "Bender Medsystems" (Austria) and catalase "Cayman Chemical" (USA). Total antioxidant activity (AOA) was detected by a method based on the degree of inhibition of ascorbate – and ferroinduced oxidation of twin-80 to MDA. The level of stable metabolites of nitric oxide (SMNO) was detected using a set for solid-phase enzyme immunoassay by R&D (England).

In addition, plasma levels of neopterin "IBL" (Germany), endothelin-1 (EN-1)"Biomedica" (Slovakia) and erythropoietin "Biomerica" (USA) were determined by enzyme immunoassay. Ceruloplasmin (CP) was determined by immunoturbidimetry using the sentinel kit (Spain), and C-reactive protein (CRP) using the Vector-Best kit (Russia) using the BTS-350 semi-automatic analyzer (BioSystems, Spain).

Cytokines (TNFα, IL-1β, IL-6, IL-8, IFNγ, IL-2, IL-17, IL-18, G-CSF, IL-4, IL-10, IL-1RA) were detected by solid-phase enzyme immunoassay using sets of Vector – best CJSC (Russia), components of the complement system (C3, C3A, C4, C5, C5A) and factor H-diagnostic set of Cytokine Ltd (Russia). The activity of the C1-inhibitor was determined by chromogenic method based on the ability to inhibit C1-esterase. Registration of all the results of enzyme immunoassay was performed using a microplate photometer "Sunrise", Tecan (Austria).

The phagocytic activity of polymorphonuclear blood leukocytes after their isolation from the blood on the phycoll-urographin density gradient (d = 1,077) was evaluated by determining the phagocytic index, phagocytic number, and phagocytosis activity index. The activity of oxygen-dependent neutrophil systems was evaluated using a PD 303 SApel spectrophotometer (Japan) based on the nitrosine tetrazolium reduction reaction (nst-test), spontaneous and stimulated by zymosan, the stimulation index and the functional reserve of neutrophils.

In statistical processing results, the χ^2 (Chi-square) was used to compare qualitative parameters. The Shapiro–Wilk test was used to assess whether quantitative features belong to a distribution type. The student's t-test was used to compare normally distributed values. The statistical significance of differences in quantitative values with an abnormal distribution was assessed using the Mann–Whitney U-test and the Wilcoxon test (when comparing dependent groups). The values of normally distributed quantitative parameters are represented by the arithmetic mean (M) with the error of the arithmetic mean (m), and abnormally distributed ones are represented by the median (Me) with an interquartile interval ($Q_{0.25}$-$Q_{0.75}$). Relationships were established based on factor analysis, cluster analysis, and Spearman's rank correlation coefficient (Gubler E.V., Genkin A.A., 1973; Lakin G.F., 1980). Differences were considered statistically significant at $p < 0.05$

Results and discussion

All drugs were administered according to the recommendations set out in the Federal guidelines for the use of medicines (formulary system) edited by A.G. Chuchalin, V.V. Yasnetsov (Moscow, 2014-2016) and in the national guidelines "Neurology" edited by E.I. Gusev, A.N. Konovalov, and A.B. Geht (Moscow, 2016).

TABLE 1. DISTRIBUTION OF PATIENTS BY THE EFFECTIVENESS OF THE PHARMACOTHERAPY

No. Group	Pharmacotherapy	Effectiveness	
		Maximum	Minimum
Chronic brain ischemia stage I			
1	Ceretone and Actovegin	6	6
2	Cerakson and Mexicor	6	6
3	Cerakson, Mexicor and Glutoxim	7	7
4	Cerakson, Mexicor and Polyoxidonium	7	7
Chronic brain ischemia stage II			
1	Ceretone and Actovegin	6	6
2	Cerakson and Mexicor	6	6
3	Cerakson, Mexicor and Glutoxim	7	7
4	Cerakson, Mexicor and Polyoxidonium	7	7

TABLE 2. NUMBER OF IMMUNE AND METABOLIC INDICATORS STATUS, DIFFERENT IN PATIENTS WITH CHEB DEPENDING ON EFFECTIVENESS OF PHARMACOTHERAPY

Group of patients	Immune status		Metabolic status of the plasma		Metabolic parameters of red blood cells	
	Σ	p < 0.05	Σ	p < 0.05	Σ	p < 0.05
Chronic brain ischemia stage I						
Ceretone and Actovegin or Cerakson and Mexicor	27	IL-8	11	G-CSF	8	
Cerakson, Mexicor and Glutoxim or Cerakson, Mexicor and Polyoxidonium		IL-10		SMNO AGP		SEG
Chronic brain ischemia stage II						
Ceretone and Actovegin or Cerakson and Mexicor	27		11		8	
Cerakson, Mexicor and Glutoxim or Cerakson, Mexicor and Polyoxidonium		TNFα IL-10		AGP		SEG AGP

To personalize the presented pharmacological treatment regimens for patients with CHEB, each of the patient groups was further divided into 2 subgroups depending on laboratory and clinical corrective effectiveness: maximum and minimum (Table 1).

In order to obtain reliable differences, we combined groups of patients who received Ceretone and Actovegin with patients who received Cerakson and Mexicor, and patients with prescription Cerakson, Mexicor and Glutoxim with patients who received Cerakson, Mexicor and Polyoxidonium [3, 4, 6, 7].

We compared the indicators of immune and metabolic status before treatment in patients with CHEB with maximum and minimum clinical and laboratory effectiveness (Table 1).

Found that patients CHEB I, receiving Cereton or Actovegin and Ceraxon and Mexicor with maximum clinical effect of the pharmacotherapy of the 27 in-

dicators of immune status before treatment, only one indicator differed from a group of patients with minimal clinical and laboratory effect (IL-8); of the 11 indicators of the metabolic status of a great figure was the same one (G-CSF) (Table 1).

Patients CHEB I, treated with Ceraxon, Mexicor and Glutoxim or Ceraxon, Mexicor and Polyoxidonium, with maximum clinical-laboratory effect from the conducted pharmacotherapy of the 27 indicators of the immune status before treatment 1 was different from groups of patients with minimal clinical and laboratory effect (IL-10); the 11 indicators of the metabolic status of quality indicators were 2 (SMNO and AGP); the 8 indicators of the metabolic status of erythrocytes is an excellent indicator there was only one (SEG) (Table 2).

Patients CHEB II, receiving Cereton or Actovegin and Ceraxon and Mexicor with maximum clinical effect of the pharmacotherapy, indicators, to treatment different from patients with minimal clinical and laboratory effect was not (Table 2).

Patients CHEB II treated with Ceraxon, Mexicor and Glutoxim or Ceraxon, Mexicor and Polyoxidonium, with maximum clinical-laboratory effect of the pharmacotherapy: the 27 indicators of the immune status before treatment 2 was different from the group of patients with minimal clinical and laboratory effect (TNFα and IL-10); the 11 indicators of the metabolic status great was 1 indicator (AGP); the indicators of metabolic status of erythrocytes were excellent 2 indicator (SEG, and AGP) (Table 2).

So, the following fact that the results of the correlation, cluster and factorial analyses are the most informative in the correctional effectiveness of clinical and laboratory parameters in chronic cerebral ischemia stage I has a definition in the plasma concentration of the cytokines TNFα, IL-8, IL-10, stable metabolites of nitric oxide and sorption capacity of the glycocalyx of erythrocytes, and with stage II disease – plasma levels of TNFα, IL-8, IL-17, IL-10, neutrophil phagocytic number and glycocalyx sorption capacity [5, 6, 7, 8], so we selected these parameters for a more detailed analysis.

In patients with CHEB I who received Cereton and Actovegin or Cerakson and Mexicor, a significantly higher concentration of IL-8 in blood plasma is determined from the minimal effectiveness of the treatment than in patients with the maximum clinical and laboratory effectiveness after the treatment.

In patients with CHEB II who received Cerakson, Mexicor and Glutoxim or Cerakson, Mexicor and polyoxidonium, with minimal effectiveness of the treatment, lower plasma concentrations of TNFα, IL-10 and higher SEG values were reliably determined than in patients with maximum clinical and laboratory effectiveness of the treatment.

Thus, it can be stated that in patients with CHEB I with high concentrations of IL-8, IL-10, SMNO and low SEG, the reception of Ceretone and Actovegin or Cerakson and Mexicor will be insufficient for effective correction of immunometabolic disorders, which requires additional administration of immunomodulator to the pharmacotherapy of scheme.

Patients with CHEB II who have higher plasma levels of TNFα, IL-10 and low SEG values should be prescribed Cerakson, Mexicor and Glutoxim or Cerakson, Mexicor and Polyoxidonium in order to obtain the maximum clinical and laboratory positive effect.

The obtained results indicate the possibility and prospects of using the principle of personalized pharmacotherapy in the treatment of patients with CHEB.

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