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Pharmacodynamic Properties of Drugs Widely Used in the Treatment of Psychosomatic Conditions

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Abstract: Lack of knowledge about the ways of formation of therapeutic effects of combined neuroprotective therapy, depending on the severity of clinical manifestations of ischemic strokes, indicates the relevance of this study. This article analyzes the effect characteristics of some neuroprotective drugs.

Keywords: vertebrobasilar bassen, arterial hypertension, neuroprotective therapy, stroke.

Despite the fact that the effectiveness of many drugs has been demonstrated in experimental studies, in clinical settings, cases of proven effectiveness of neuroprotective drugs are rare. This is due to the etiological, pathogenetic and clinical heterogeneity of ischemic stroke, as well as the presence of patients with concomitant diseases that aggravate the course of stroke and prevent the directed action of neuroprotective agents. Thus, the presence of arterial hypertension, diabetes mellitus, heart failure, etc., affects the structure of the blood-brain barrier, collateral blood circulation, cellular metabolism, and the neuroimmune system. Due to these and a number of other factors, drugs that are effective under experimental conditions do not confirm their effect in the clinic.

Analysis of the dynamics of the deployment of molecular and biochemical mechanisms triggered by acute focal cerebral ischemia has established a clear time sequence of their "activation". During the first 3 hours from the moment of acute cerebrovascular accident, the maximum energy deficit in the ischemic tissue is presented; after 3-6 hours - glutamate-calcium excitotoxicity and lactic acidosis, fading away by the end of the 1st day [5].

Such consequences of ischemia as oxidative stress, local inflammation, secondary microcirculatory disorders in the focus of ischemia, increased permeability of the blood-brain barrier, autoimmune reactions begin to manifest themselves in 2-3 hours, reaching a maximum in 12-36 hours. The process of apoptosis is maximally pronounced by 2-3 days. The consequences of ischemia persist for a long time - for several months, contributing to the progression of dystrophic processes and the development of encephalopathy in the post-stroke period [6].

Each step of the ischemic cascade is a potential target for therapeutic interventions. The earlier the cascade is interrupted, the greater the effect can be expected from treatment [7]. Currently, there are several goals in the fight for the survival of brain cells [9]: a decrease in glutamate expression, normalization of ion channels, restoration of phosphatidylcholine levels, and a decrease in the level of arachidonic acid and other inflammatory mediators.

A variety of mechanisms for the formation of cerebral infarction makes it possible to fairly conditionally distinguish two main directions of neuroprotective therapy: primary and secondary neuroprotection [8].

Primary neuroprotection is aimed at interrupting the rapid mechanisms of necrotic cell death - reactions of the glutamate-calcium cascade; it should be applied from the first minutes of ischemia and continue during the first 3 days of stroke [12]. Secondary neuroprotection is aimed at reducing the severity of the long-term consequences of ischemia, it can be started 3-6 hours after the development of a stroke and continue for at least a week [11]. It is proposed to use magnesium sulfate and glycine as primary neuroprotectors, methionyl-glutamyl-histidyl-phenylalanine-prolyl-glycyl-proline, ethylmethylhydroxypyridine succinate, cytoflavin as secondary ones [13].

Subsequent treatment should be aimed at activating regenerative processes. The neuroprotective effects of drugs are manifested in an increase in the resistance of brain cells to hypoxia and ischemia; correcting the level of cellular energy; improving blood supply to the brain; increasing the functional activity of neurons and glial cells; normalization of mediator imbalance [4].

Cytoflavin. The combined preparation Cytoflavin, developed by domestic scientists, contains succinic acid, nicotinamide, inosine, riboflavin. Methylglucamine, a specially synthesized intracellular carrier, allows delivery of all components of cytoflavin not only intracellularly, but also intracellularly, which significantly increases the effectiveness of the drug [4, 37-39].

Cytoflavin components have a mutually potentiating effect, increasing energy production in all types of cells, and above all in the cells of the central nervous system. The main component of cytoflavin is succinic acid, a participant in the reactions of the Krebs cycle [3]. Its high content allows Cytoflavin to exert a significant energy-correcting effect during hypoxia and classify the drug as an antihypoxant [8]. Nicotinamide and riboflavin, which are part of the drug, serve as coenzymes in glycolysis reactions under conditions of hypoxia and ischemia. The mild vasodilating, central anti-inflammatory and neuroprotective effect of cytoflavin is due to the presence of inosine in its composition and the effect on the adenosine receptor systems [2].

An important property of Cytoflavin is precisely the fact that its antihypoxic and antioxidant effect is manifested under conditions of ischemia [6].

The clinical efficacy of Cytoflavin in stroke is manifested significantly faster, compared with the comparison groups, with regression of general cerebral symptoms and recovery of motor and sensory functions. It has been studied in several multicenter studies, which made it possible to recommend its use both in the hospital and at the prehospital stage [10].

Many authors note the need for early prescription of drugs that protect the cell cluster from hypoxia. Early administration of Cytoflavin showed the greatest dynamics of regression of focal symptoms, both in ischemic and hemorrhagic stroke [4]. With IS, the drug has shown its effectiveness in reducing mortality. Mortality in the group of patients receiving Cytoflavin was 8%; in the comparison group - 12%, while the duration of patients' stay in the intensive care unit was reduced [10].

In a clinical and instrumental randomized comparative prospective study, which included patients with hemispheric ischemic stroke, it was shown that the addition of Cytoflavin to the standard treatment regimen leads to a significant improvement in not only clinical but also paraclinical parameters. Thus, the use of this drug led to a more rapid recovery of consciousness, regression of focal neurological symptoms, and an early decrease in disability. In the cytoflavin group, by day 21 of therapy, the ischemic zone, according to MRI data, was, on average, 1.1 times less than at baseline. In patients who received only basic therapy, by day 21, the lesion focus increased 1.4 times. The study also revealed the features of the dynamics of free radical processes and the positive effect of cytoflavin therapy on the indicators of markers of oxidative stress [12].

Choline alfoscerate. Choline alfoscerate - gliatilin - is a centrally acting cholinomimetic. When using this drug, choline is released from the active substance in the brain, where choline is involved in the biosynthesis of acetylcholine, and alfoscerate serves as a source of phosphatidylcholine formation [5].

Acetylcholine is the main neurotransmitter. Phosphatidylcholine is a key phospholipid of cell membranes, its content in the membranes of CNS neurons in humans is almost 50% [11]. The

formation of phosphatidylcholine is associated with glycolysis and oxidative phosphorylation. Under conditions of ischemia and hypoxia, phosphatidylcholine is intensively hydrolyzed, due to which the composition, skeleton and matrix function of cell membranes are sequentially disrupted, which leads to cell death [12]

Gliatilin also increases cerebral blood flow, enhances metabolic processes and activates the structures of the reticular formation of the brain, and helps to reduce excitotoxicity [8].

The therapeutic effect of gliatilin in ischemic stroke has been studied in sufficient detail [10]. The administration of gliatilin in an isolated form, 1 g for 5 days of the acute period of IS, has a beneficial effect on the clinical dynamics of the disease as a whole (early recovery of consciousness, regression of paresis, restoration of speech and productive thinking), leads to a decrease in neurological deficit and an increase in patients' ability to self-care , which is associated with a smaller final volume of brain damage [7].

In acute cerebrovascular disorders, the drug prevents the expansion of the penumbra zone, actively dose-dependently restores consciousness, reduces cognitive impairment in the recovery period, increases the ability of patients to self-care and reduces the incidence of pulmonary complications [15].

Actovegin is a highly purified hemodialysate obtained by ultrafiltration from the blood of calves. Actovegin contains compounds with high biological activity: amino acids, oligopeptides, nucleosides, oligosaccharides, glycolipids, trace elements. The technology of hemodialysate production excludes the presence of protein and other components with antigenic or pyrogenic properties [9].

The basis of the pharmacological action of Actovegin is the improvement of glucose transport and oxygen uptake in tissues, which increases the energy potential of the cell, stabilizes the plasma membranes of cells during ischemia [50, 56-60]. Under the influence of Actovegin, the metabolism of high-energy phosphates increases; enzymes of oxidative phosphorylation are activated; the lysosomal activity of the cell increases; the synthesis of carbohydrates and proteins is accelerated; the influx of potassium ions into the cell increases, potassium-dependent enzymes are activated; the breakdown of the products of anaerobic glycolysis is accelerated, and the level of lactate decreases [17].

The effect of the drug after parenteral administration is manifested within the first 30 minutes. The leading mechanism of action of Actovegin in ischemic stroke is the activation of aerobic and anaerobic oxidation, improvement of cerebral microcirculation, and increased resistance of brain structures to hypoxia. The active components of the drug also have an insulin-like effect.

The use of Actovegin against the background of hemodilution at a dose of 1000 mg per day in patients with severe stroke under conditions of neuroresuscitation showed a significant improvement in the clinical state, activation of consciousness, stabilization of indicators of neurological status, relief of respiratory disorders without the use of mechanical ventilation [4]. According to EEG monitoring data against the background of Actovegin use, an increase in the EEG power spectrum in the range of fast and slow waves was noted, which preceded the activation of consciousness. Mortality in the group of patients receiving Actovegin ranged from 7 to 14%, depending on the period from the onset of stroke to admission to the hospital. In the control group, the mortality rate reached 22% [14].

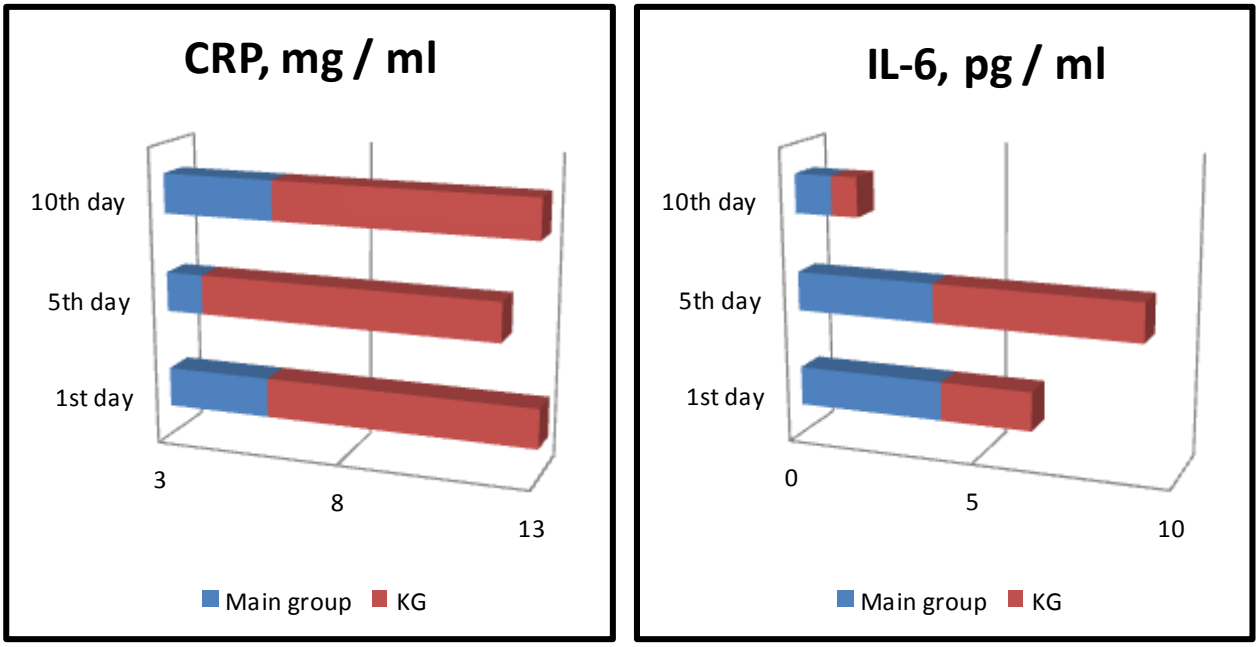
Purpose of the study: to study the effectiveness of treatment of ischemic stroke in the acute period with a complex of neuroprotective drugs.

Materials and methods Clinical observations were carried out in the clinic of neurological diseases of the Bukhara State Medical Institute on the basis of the Bukhara City Clinical Hospital

We for the period 2019–2023. 154 patients with IS in the acute period were examined at the age of 41 - 81 years (average age 60.56 ± 0.60 years), of which there were 101 men, 53 women. The average age of the observed men was 60.63 ± 0.77 years, women - 60.42 ± 0.94 years.

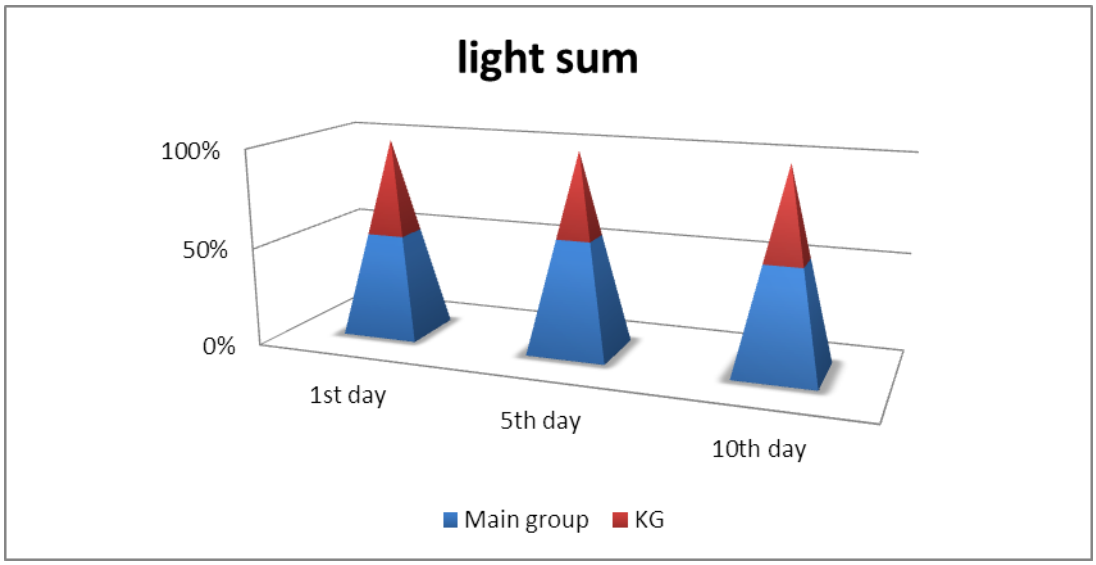
The levels of indicators of inflammation in the acute period of IS in VBD are shown in Figure 4.17. CRP had multidirectional dynamics in the groups: by the 5th day it increased in the control and decreased in the main one, but by the 10th day it returned to the initial level. The level of IL-6 in the main group gradually decreased during the first 10 days, in the control group it increased by the 5th day, and then also decreased. In the CG, there was a tendency to a concomitant change in proinflammatory IL-6 and acute phase CRP.

Dynamics of CRP and IL-6 in the main and control groups of IS in VBB



CL indices in the acute period tended to increase by the 5th day, followed by a decrease in both groups (Fig. 4.18). A correlation was found between the chemiluminescence index on the first day and the severity of stroke on the NIHSS scales on the first day (Spearman R = 0.94, p = 0.05).

The dynamics of the CL index in the main and control groups of II in VBD



The parameters of cerebral hemodynamics according to the TCD data in the main and control groups differed in little variability during the observation period: the maximum systolic velocity, the velocity at the end of the diastolic cycle, and the average velocity per cardiac cycle did not change significantly over time.

Initially, patients in the study and control groups had comparable neurological deficits according to the NIHSS and Original scales. In the group of patients who received a combination of

neuroprotective agents, a significant regression of focal symptoms was obtained by the 5th day of treatment, but further significant changes in neurological status were not observed.

In the CG, statistically significant improvement occurred by the 10th day. By the end of inpatient treatment, the main group and the CG had a comparable severity of stroke. Lethal cases were not registered in the main group, two patients died in the control group.

By the time of discharge in the main group, there was a greater percentage of observations with a slight degree of dependence on others. A better recovery was shown against the background of combination therapy in younger patients. There was no significant difference in the indices of intracranial blood flow and CL between the main and control groups. In the CG, there was a tendency to unidirectional change in the parameters of inflammation.

Thus, we have not received strong evidence of the advantages of combined neuroprotective therapy for IS in VBB compared with standard therapy in surviving patients. However, the advantages of the proposed treatment regimen were in a faster response to therapy, the absence of deaths, and a higher percentage of patients with mild dependence on others upon discharge from the hospital.

CONCLUSIONS.

1. Combined neuroprotective therapy using gliatilin, cytoflavin and actovegin in the acute period of ischemic stroke showed a more pronounced therapeutic effect compared to standard treatment. Hospital mortality in the main group was 2.35%, in the control - 8.70%. The greatest recovery of neurological functions by the end of the acute period of stroke was observed in patients of the main group with IS in moderate CB.
2. Combined neuroprotective therapy in IS in VBD turned out to be less effective: regression of points on the NIHSS scale by the end of the acute period was 3 [1; 7] points, while in IS in KB - 4 [2.5; 5].
3. Based on the dynamics of the serum content of brain neurotrophic factor (BDNF), a significant tendency to an increase in its concentration by 6.4% with combined neuroprotective therapy was revealed, while against the background of standard therapy this indicator decreased by 4.6%.

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