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The Use of Neurotropin in the Treatment of Ischemic Strokes

Sikorska MV[1], Vizir IV[1], Belenichev IF[2], Laponov OV[1] and Popazova OO[3]*

[1]Department of Nervous Diseases, Zaporizhzhia State Medical University, Ukraine
[2]Department of Pharmacology and Medical Formulation with Course of Normal Physiology, Zaporizhzhia State Medical University, Ukraine
[3]Department of Histology, Cytology and Embryology, Zaporizhzhia State Medical University, Ukraine

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***Corresponding author:** Olena Popazova, Department of Histology, Cytology and Embryology, Zaporizhzhia State Medical University, Ukraine, Tel: +38(096)-472-62-50; Email: popazova.ea@gmail.com

Abstract

This research analyzed the results of treatment of 32 patients with ischemic stroke with the drug neurotropin, an antioxidant with antihypoxant properties, evaluated its clinical efficacy, the effect on the processes of protein oxidative modification, and the antioxidant activity of the blood. The control group consisted of 15 people, in whose traditional therapy neurotropin was not included. The study showed that the use of neurotropin in complex therapy contributed to the regression of neurological deficit, caused a positive effect on the oxidative metabolism of the brain, hemostasis, and had a hypolipidemic effect. Thus, the inclusion of neurotrophin in the complex therapy of ischemic strokes is reasonable and expedient.

Keywords: Ischemic Stroke; Oxidizing Metabolism of Brain Treatment

Introduction

Despite considerable advances in modern angioneurology, the problem of acute cerebrovascular accident (ACVA) continues to retain extraordinary medical and social significance [1-5]. Stroke is the second leading cause of death and the leading cause of disability among people in the European Union, North America and Japan, creating a serious burden on the health care system, economy and and the whole society [6-8]. Analysis of the literature of the last 5-7. Years indicates the positive effects of the use of neuroprotectors at the prehospital and hospital stages of the treatment of ischemic stroke [9,10]. But unfortunately, basic nootropic and neurometabolism drugs don't always have the expected neuroprotective effect in the acute period of cerebral ischemia [11-13]. In this regard, it is extremely important to apply a scientifically based approach for the rational choice of drugs designed to optimize standard therapy. Studies of recent decades have established that one of the links in the pathogenesis of brain neurodestruction is the hyperproduction of reactive oxygen species (superoxide radical, hydroxyl radical, peroxynitrite anion, hypochlorite anion, etc.) by bioenergetic and neurochemical systems of the cell, which leads to oxidative modification and destruction of proteins, lipids and nucleic acids. Such disorders alter the protein and lipid fragments of neuronal membranes, initiate apoptotic processes and the development of inflammatory reactions, impair the sensitivity and specificity of receptors, the generation, creation and conduction of nerve impulses, disrupt synaptic conduction and, finally, lead to the development of cognitive deficit or brain death. Therefore, a more detailed study of molecular biochemical lesions of the brain in ACVA and the development of new approaches to targeted neuroprotection, one of the promising targets of which is considered to be ROS/NO-dependent mechanisms of neuronal damage [14,15], determines the relevance of this

research with the possibility of using the results obtained in clinical practice [16-19]. Thus, inhibition of hyperproduction of ROS and cytoxic NO metabolites, leads to inhibition of oxidative modification and inactivation of protein macromolecules of key enzymes of bioenergetic processes of the neuron [20,21], hyperpolarization of mitochondrial membranes, disruption of the thiosulfide system of red-oxi mechanisms - regulation, oxidative modification of nucleic acids, thereby preventing inhibition of the expression of genes responsible for the synthesis of a number of enzymes of oxidative metabolism [22-24]. In addition, a decrease in ROS hyperproduction is promising for inhibition of neuroapoptosis and a decrease in the severity of cognitive deficit in post-stroke patients [12]. Pharmacological correction of ROS production in cerebral ischemia and inhibition of oxidative stress reactions can lead to a decrease in ultrastructural and functional signs of secondary mitochondrial dysfunction [25]. All this contributes to the restoration of the energy metabolism of the brain, inhibition of mitoptosis [11-13,26-31]. Currently, in clinical practice, a large number of drugs with an antioxidant effect are used as secondary neuroprotectors with properties-emoxipin, thiotriazoline, trollox, quercetin, selenase, glutathione [32-34].

Drugs with antioxidant and antihypoxic action include the drug Neurotropin (succinate-2-ethyl-6-methyl-3-hydroxypyridine) in terms of chemical structure, it is a salt of succinic acid (succinate) and belongs to the group of synthetic antioxidants. In conditions of ischemic damage to brain tissue, Neurotrophin inhibits the production of free radicals, reduces LOP activation Neurotropin also has a hypolipidemic effect - it reduces low-density lipoproteins and total cholesterol level [35,36].

Thus, the mechanism of action of neurotrophin is determined by antioxidant properties, the ability to stabilize cell biomembranes, activate the energy-synthesizing functions of mitochondria, and improve synaptic transmission and interstructural interactions of the brain.

The purpose of this work is to evaluate the clinical efficacy of an antioxidant with antihypoxanic properties of neurotropin and its effect on FRO processes and oxidative modification of the protein of antioxidant activity of blood in the treatment of 32 patients with atherothrombotic and cardioembolic subtypes of hemispheric ischemic stroke.

Materials and Research Methods

This study involved 32 patients (17 men and 15 women) aged 47 to 76 years with acute ischemic stroke. The main vascular disease in 14 patients was atherosclerosis of the vessels, in 12-hypertensive disease in combination with atherosclerosis in 6-hypertension. The diagnosis of ischemic stroke was made on the basis of neurological examination, laboratory results and spectral computed tomography (SCT). Patients were admitted within the first 12 hours after the onset of the stroke. Persons from the concomitant side of other organs and systems were excluded from the research.

The severity of neurological dysfunctions was assessed during hospitalization of patients and at the end of therapy on days 20-21 according to the NIHSS scale (National Institutes of Health Stroke Seale, USA). The degree of post-stroke disability was assessed using a modified Rankin scale. All patients who took part in the study underwent standard laboratory tests: a clinical blood test, blood glucose levels, hematocrit, cholesterol, LDL, urea, and creatinine were determined.

Furthermore, markers of oxidative modification of proteins were determined in blood plasma of all patients on the first day and at the end of treatment (20 days)-aldehydephenylhydrazone (APH) and ketonephenylhydrazone (CPH) based on the interaction of oxidized amino acid residues with 2,4-dinitrophenylhydrazine (2,4-DNPH) and the formation of aldehyde phenylhydrazones (APH) and carboxylphenylhydrazone (CPH), having an absorption spectrum at 274 nm 363 nm, respectively, on a spectrophotometer Libra S 32 PC(UK).

The level of homocysteine was determined in blood plasma, the activity of superoxide dismutase in the hemolysate was determined on an automatic biochemical analyzer Prestige24i (BCM Diagnostics). The level of methionine and cysteine in blood plasma after chromatographic purification was determined spectrophotometrically during the formation of a complex with ninhydrin [37,38]. Determining spectrophotometrically in the hemolysate adenyl nucleotides, malate and the activity of succinate dehydrogenase (SDH) and cytochrome C oxidase (CCO) [37,38].

In addition to the above, all patients underwent transcranial Doppler sonography (TCD) of the head vessels at the beginning and at the end of treatment. Patients of the main clinical group received traditional therapy (anticoagulants, magnesium sulfate, antiplatelet agents, citicoline, antihypertensive drugs, if necessary) in combination with the drug neurotropin (RUE “Bulmedpreparat”, Republic of Belarus), which in the acute period of stroke (1-5 days) was prescribed 300 mg intravenously drip 1 time per day in 200.0 isotonic sodium chloride solution, then the treatment was continued at a dose of 100 mg intramuscularly for 10-14 days.

The control group consisted of 15 patients with ischemic hemispheric stroke who received only conventional therapy.

The patients of both groups were comparable in terms of demographic characteristics, the degree of impairment of neurological functions, and the localization of the ischemic focus. The research results were processed using the statistical package of the licensed program "STATISTICA® for Windows 6.0» (StatSoft Inc., № AXXR712D833214FAN5) and «SPSS 16.0», «Microsoft Excel 2003». Certain statistical procedures and algorithms are implemented as specially written macros in the corresponding programs. For all types of analysis, the differences were considered statistically significant at $p < 0.05$.

Results and Discussion

In 21 patients, an ischemic stroke in the carotid basin was of sufficient size> 16 mm in diameter, in 9-small carotid infarctions. Taking into account the mechanisms and reasons for the development of ACVA, the TOAST criteria were used to identify the subtypes of ischemic stroke: atherothrombotic (n = 19), cardioembolic (n = 8), and infarction of unknown cause (n = 5).

Analysis of the baseline level of neurological deficit according to the NIHSS scale in the examined patients showed that 11 patients had mild neurological dysfunctions (<9 points, on average 4,17+0,4 points), in 9 - moderate (> 9 points, on average 9.25+0.6 points), in 12 patients - severe (> 13 points, on average 15.16+0.8 points). The total neurological deficit in the group as a whole was 9.61+1.1, which corresponds to moderate dysfunction.

According to the modified Rankin scale, before treatment, 13 patients had mild disability (2 points), in 3 patients-moderate disability, patients needed outside help, but could move independently (3 points), 9- moderate severe disability, patients could not move without assistance (4 points), 7-severe disability, patients needed outside help (5 points).

As a result of the therapy with Neurotropin in combination with traditional treatment, 8 patients (25%) with an initial neurological deficit of mild severity showed a complete recovery of the lost functions on days 15-21. By days 20-21, another 11 patients (34.4%) showed a significant regression of neurological deficit to a mild degree (in cases with concomitant moderate deficiency). Of the 12 patients with severe neurological deficit, the condition of 5 improved to moderate severity, in 5 patients by the end of treatment the condition remained severe, and in two cases a fatal outcome occurred (in both cases, there was a massive ischemic stroke). The total neurological deficit in patients with non-fatal ischemic stroke on the NIHSS scale was 5,46+0,7 points ($p<0,05$) (in the control group 6,13+0,6 points). There was also a decrease in post-stroke disability according to the modified Rankin scale to 1,8+0,06 points.

To assess the severity of ischemic damage to brain tissue and the effectiveness of neurotrophin, studies of the state of free radical oxidation processes in blood plasma were carried out; in particular, it is known that markers of oxidative destruction of proteins are the earliest markers of oxidative damage to functional macromolecules. Analysis of parameters showed that before treatment, the level of APH was 2.7 times exceeded the indicators of healthy persons, and that of CPH was 18 times higher. APH on the first day was, respectively, group 1-12.7+0.87 c.u./l of protein, group 2-11.9+0.76 c.u./l of protein; after the course of neurotropin, the indices decreased, respectively, to 11.3+0.75 c.u./l and 10.1+0.71 c.u./l, however, the level of healthy people still did not reach. CPH indicators on the first day were 36.5+3.8 in the first group and 38.8+2.79 in the second; after the treatment in the 2nd group, who took neurotropin, the values decreased to 16.4+0.5 c.u./l, while in the 1st group they remained high 26.4+3.41 c.u./l.

The activity of the enzyme of the antioxidant system of superoxide dismutase on the first day of the disease was reduced in both groups accordingly (76.3+3.15 c.u.(mg/protein)/min and 78.2+3.7 c.u.(mg/protein)/min compared with the group of healthy individuals; after treatment, there was a significant increase in the level of SOD activity in the group of patients taking neurotropin up to 112.7+12.2 c.u.(mg/protein)/min, in the group of patients with traditional treatment indicators by the end of treatment increased to 91.3+9.8 c.u.(mg/protein)/min.

According to recent studies, the ratio of the thiol-disulfide system, in conditions of cerebral ischemia, is a determining factor in the development of a cascade of pathobiochemical reactions, the formation of mitochondrial dysfunction and cell death. It is known that hyperhomocysteinemia is a leading factor in oxidative stress in the brain.

The molecular consequences of increasing the concentration of homocysteine include: intensification of methylation of nucleic acids, proteins, phospholipids; increase the intracellular level of free radicals, modification of glutamant [38]. Also, to study the thiol-disulfide system, we studied not only the content of its oxidative products, but also the concentration of its reducing thiol intermediates (cysteine and methionine), which reflects the effect of neurotropin on the balance of the thiol-disulfide system in ischemic stroke.

The research results are presented in Table 1.

Indicators	1 day		20 days	
	Patients with traditional therapies	Patients receiving neurotropin	Patients with traditional therapies	Patients receiving neurotropin
Cysteine, μm/ml	15,7±1,82	14,9±1,36	16,4±2,0	18,1±3,52
Methionine, μm/ml	12,8±1,86	13,1±1,94	13,8±1,86	15,6±1,64
Homocysteine, μm/ml	34,3±3,72	32,7±4,12	21,6±2,63	18,4±1,72

Table 1: Dynamics of indicators of the thiol-disulfide system of the brain in ischemic stroke in conditions of treatment with neurotropin.

As can be seen from the data presented, the indicators in the group of patients who received neurotropin in complex therapy have a more pronounced tendency to normalize by the end of treatment. Energy deficiency, coupled with the activation of free radical processes, is one of the most important components that cause structural and functional damage to the cells of the nervous tissue in ischemic strokes. The total effect of energy deficiency, a change in oxygen transport and oxidative modification of macromolecules lead to a sharp change in the activity of a neuron, and then to its death [39,40]. This is evidenced by changes in the content of adenyl nucleotides, in particular, ATP, the content of malate, and the level of activity of succinate dehydrogenase (SDH) and CCO.

The use of neurotropin had a positive effect on the indicators of energy metabolism (Table 2), increasing the level of ATP, malate and enzyme activity to a greater extent than in the comparison group, however, it should be noted that they did not reach the indices of healthy persons.

	Patients receiving conventional therapy		Patients receiving neurotropin and conventional therapy	
Indicators	1 day	20 days	1 day	20 days
ATP, μm/ml	1,56±0,02	1,94±0,17	1,48±0,02	2,63±0,03
Malate, μm/ml	0,28±0,01	0,31±0,02	0,21±0,01	0,41±0,03
SDH, nm/mg/min	6,82±0,16	10,11±0,21	7,61±0,12	12,83±0,09
CCO, μm/mg/min	11,9±0,76	12,96±1,12	12,22±0,81	17,6±1,74

Table 2: Dynamics of indicators of energy metabolism.

Thus, according to the results of our studies, it can be assumed that the mechanism of the neuroprotective action of Mexidol is its direct mitoprotective activity, which is realized, both through a positive effect on the state of the thiol-disulfide system and modulation of the opening of the mitochondrial pore (which occurs due to the oxidation of thiol groups of the cysteine-dependent site protein of the inner membrane of mitochondria (ATP/ADP-antiporter), and due to direct energotropic action (Intensification of oxidative energy production).

Analysis of the state of cerebral hemodynamics in patients before treatment showed an increase in the thickness of the intima-media complex and the common carotid artery, a decrease in the linear systolic blood flow velocity, and an increase in the indices of resistance and peripheral resistance in individual vessels of the carotid and vertebral-basilar basins. According to TDC data, the therapy performed increased the maximum average blood flow velocity on the side of the ischemic focus and in the vessels of the intact cerebral hemisphere; however, these changes did not have significant differences, both in the compared groups of patients and at the beginning and at the end of therapy.

In patients with ischemic hemispheric stroke who received neurotropin, changes in lipid metabolism were determined, which confirms the hypoglycemic effect of the drug. There was a significant decrease in the level of total cholesterol from 6,09+0,17 mmol/l to 4,69+0,20 mmol/l; low density lipoproteins from 4,28+0,20 mmol/l to 3,21+0,3 mmol/l ($p<0,05$). Changes in the indicators of high density lipoproteins and triglycerides tended to normalize and did not significantly differ in the study and control groups of patients.

As a result of the therapy with neurotropin, positive changes in the hemostatic system were noted. So the level of fibrinogen decreased from 4.1+0.5 to 2.3+0.3 g/l, and MT from 100.2+2.7% to 83.23+3%, which reduced blood viscosity and improved cerebral blood circulation in the microcirculation system. Thus, the inclusion of neurotrophin in the complex therapy of ischemic hemispheric stroke

increased the degree of regression of impaired neurological functions.

Our data are consistent with our experimental studies, which showed that the administration of neurotropin (Mexidol) to rats with ligation of the common coon arteries at a dose of 250 mg/kg for 21 days had a significant effect. Oral administration of neurotropin (Mexidol) in animals to a decrease in levels of oxidative DNA and protein modification markers, and to a decrease in NO hyperproduction and formation of nitrotyrosine. Mexidol changed an intensity of immediate early gene cFos expression and increased a concentration of Bcl-2 in neurons of IV-V cortex layers, and also reduces the density of apoptotic neurons. Neurotrophin (Mexidol) lessened an expressiveness of cognitive and memory function in rats with with ligation of the common carotid arteries. An influence of Mexidol on expression of c-Fos and concentration of Bcl-2 in neurons of rats with cerebral ischemia can explain the mechanism of its neuroprotective activity, particularly, by an influence on such delayed mechanisms of neuronal death after stress, as apoptosis [41-44]. Neurotropin is a highly effective neuroantioxidant, inhibits the oxidative modification of protein, increases SOD activity, normalizes thiol-disulfide equilibrium, has a membrane stabilizing effect, intensifies energy production of mitochondrial function and AF synthesis.

According to a number of the studied parameters, the patients receiving the course of neurotropin significantly exceeded the analogous parameters of the patients with ACVA in the control group (basic therapy). Thus, the obtained results of clinical and biochemical studies indicate that the inclusion of a secondary neuroprotector neurotrophin in the basic therapy can improve the results of treatment.

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