DOI: 10.23934/2223-9022-2018-7-1-44-52

METABOLIC THERAPY IN PATIENTS WITH ISCHEMIC STROKE

L.B. Zavaliy[1]*, S.S. Petrikov[1], A.V. Schegolev[2]

[1] Neurological Department for patients with acute disorders of cerebral circulation with resuscitation and intensive care unit, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department, Moscow, Russian Federation
[2] Department of Anesthesiology and Critical Care, S.M. Kirov Military Medical Academy, St. Petersburg, Russian Federation

*** Contacts:** Lesya B. Zavaliy, Cand. Med. Sci., Neurologist of the Neurological Department for patients with acute disorders of cerebral circulation with resuscitation and intensive care unit N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department. Email: l.zav@bk.ru

ABSTRACT The article shows the world experience of metabolic therapy use in the treatment of ischemic stroke. The issue still remains prominent. The reasonability of prescribing metabolic drugs is not completely clear, its effectiveness has not been fully proved, despite numerous studies which show only trends. The article presents an overview of the most popular drugs of different pharmacological groups with a metabolic effect which affect different parts of the ischemic cascade. Ethylmethylhydroxypyridine succinate and cytoflavin have predominantly antihypoxic effect, improve functional outcome and neurological functions, and normalize overall well-being and adaptation. Cerebrolysin is a complex of low molecular weight biologically active peptides derived from the pig's brain. It has a multimodal effect on the brain, helps to reduce the volume of cerebral infarction, restores neurologic functions and improves the functional outcome. Cortexin is a mixture of cattle brain polypeptides, also has a complex action that provides the most complete reversion of neurological deficit, improves cognitive functions and the functional outcome, reduces the level of paroxysmal convulsive readiness and improves bioelectric activity of the brain. Citicoline is a precursor of cell membrane key ultrastructures, contributes to significant reduction in the volume of cortical brain damage, improves cholinergic transmission, which results in better clinical outcome, even despite the questionable impact on the neurological status. Choline Alfoscerate is a precursor of choline, and the use of the drug significantly limits the growth of the cerebral infarction area starting from the first day of therapy, leads to reversion of neurological symptoms and achievement of rehabilitation goals. Actovegin is deproteinized derivative of calf blood, activates metabolism in tissues, improves trophism and stimulates regeneration. In a large study, it was shown that Actovegin improved cognitive function in patients who had experienced a stroke,. The drug does not significantly improve the neurological status of patients after a stroke, but it reduces the risk of the stroke development in the next 10 years. Thus, we analyzed mechanisms of medical substances action and data of experimental and clinical studies, including ones after thrombolytic therapy and with inclusion of drugs for primary and secondary prevention of ischemic stroke. The reasonability and effectiveness of prescribing a combination of drugs of different pharmacological groups affecting brain metabolism remains controversial, since the excessive drug treatment may have complications. The safety of metabolic therapy is in doubt, and some of authors views presented confirm the need for additional large independent studies.

Keywords: stroke, ischemic stroke, cerebral infarction, acute cerebrovascular accident, metabolic therapy, neuroprotective therapy, neuroprotectants, antihypoxants

For citation Zavaliy L.B., Petrikov S.S., Schegolev A.V. Metabolic therapy in patients with ischemic stroke. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2018; 7(1): 44–52. DOI: 10.23934/2223-9022-2018-7-1-44-52 (In Russian)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments The study had no sponsorship

The use of metabolic therapy in treatment of patients with acute stroke is controversial and actively discussed in the literature. A number of clinical tests show that only metabolic therapy helps reach best results in treatment of acute cerebrovascular event [1], but some authors have questioned the efficacy of additional drug therapy [2, 3]. A complex cascade of consecutive ischemic and mutually interrelated reactions occurs with the development of cerebral infarction. As a consequence of hypoxia, the glucose splits by anaerobic way, causing lactic acidosis. Violation of the enzyme system and transport proteins functioning leads to the release of potassium ions from the cell into the extracellular space and the entrance of sodium and calcium ions into the cell. Excessive excitatory neurotransmitters causes opening of calcium channels and additional inflow of calcium ions into neurons. Excessive accumulation of calcium inside the cell activates enzymes, causes the overload of mitochondria with uncoupling of oxidative phosphorylation and intenses catabolism. The breakage of phospholipids in the outer cell membrane, as well as the membranes of intracellular structures stimulates lipid peroxidation and free radical formation. The set of reactions leads to the death of neurons.

The drugs have been developed to influence each stage: succinate-containing substances, derivatives and analogues of gamma-aminobutyric acid, amino acids and its combinations, precursors of acetylcholine, polypeptides and neuropeptides, hemoderivatives, derivatives of pyrodoxin, carnitine and pyrrolidine, anticholinesterase drugs, complex preparations.

The most popular drugs are the following metabolic substances: Ethylmethylhydroxypyridine succinat, Inosine + Nicotinamide + Riboflavin + Succinic acid, Cerebrolysin, polypeptides of cattle brain, Citicoline, Choline Alphoscerate and Actovegin.

ETHYL METHYL HYDROXYPYRIDINE SUCCINAT

Ethyl methyl hydroxypyridine succinat (Mexidol, Mexiprim, Mexicor, Neurox, Cerecard etc.) is one of the most popular drugs for prehospital, hospital and outpatient use. The drug has antihypoxic, antioxidant and membrane protective effect, inhibits lipid peroxidation, improves the quality of cell membranes, increases the rate of synaptic transmission and the concentration of dopamine in the brain, intenses the compensatory activity of aerobic glycolysis, decreases the degree of oxidative processes inhibition in the Krebs cycle under conditions of hypoxia [4], interacts with the benzodiazepine receptor complex $GABA_A$ at the neuronal level [5], and finally, significantly reduces intracellular lactate and inositol [6].

V.I. Skvortsova et al. (2006) conducted a randomized, double-blind, placebo-controlled trial of the use of ethyl methyl hydroxypyridine succinate in the acute period of ischemic stroke. The trial showed its efficacy and safety in the complex therapy of atherothrombotic and cardioembolic hemispheric ischemic stroke (300 mg per day starting from the first day of the disease, for 14 days, especially with the prescription of the drug in the first 6 hours). In patients treated with ethyl methyl hydroxypyridine succinate, a rapid regression of focal neurological deficit and an improvement of functional recovery were observed. The study of the antioxidant system showed an increase in the activity of its enzymes (superoxide dismutase, glutathione peroxidase, glutathione reductase), and the analysis of the enzymes of the mitochondrial respiratory chain revealed an increase in the activity of succinate dehydrogenase [7]. According to V.I. Seregin (2015), treatment with ethyl methyl hydroxypyridine succinate at a dose of 500 mg intravenously daily for 10 days in an acute period of severe ischemic stroke was effective and safe, improved the outcome of the disease and decreased mortality rates in comparison with the group of patients who did not receive the drug [8]. The results of several studies conducted by O.V. Androfagina et al. (2015), T.T. Kispayeva (2013), L.V. Novikova et al. (2013), M.A. Lutsky (2010) showed that the use of ethyl methyl hydroxypyridine succinate in the acute period of stroke lead to a statistically and clinically significant improvement in cognitive, motor, sensory functions, reduced fatigue, anxiety, and improved adaptation to physical exertion [9, 10, 11, 12] . O.V. Kurushina et al. (2013) proved the drug's efficacy in the treatment of autonomic nervous system dysfunction and psychoneurotic disorders in the early recovery period of ischemic stroke [13]. According to L.A. Shepankevich et al. (2016), long-term therapy with ethyl methyl hydroxypyridine succinate can optimize lipid-lowering therapy for patients with cerebral infarction on the background of diabetes mellitus [14].

According to several authors, the drug is effective for secondary prevention of strokes of various pathogenetic types. So, V.V. Kovalchuk (2014) showed that ethylmethylhydroxypyridine succinate reduced the incidence of repeated strokes, both in patients with a burdened comorbid background and without concomitant diseases [15].

The use of ethylmethylhydroxypyridine succinate in combination with thrombolytic therapy of ischemic stroke. According to Z.Y. Chefranova et al. (2012), the inclusion of an antihypoxant in the course of the baseline therapy after administration of a recombinant tissue plasminogen activator to patients with cerebral infarction creates conditions not only for restoring the neurological status, but also prevents secondary damage to the brain [16].

CYTOFLAVIN

The combined preparation Cytoflavin (Inosine+Nicotinamide+Riboflavin+Succinic Acid) participates in stimulation of cellular respiration and energy generation, improvement of oxygen utilization by tissues, restoration of enzyme activity providing antioxidant action in brain cells. The drug activates intracellular protein synthesis, promotes utilization of glucose, fatty acids, the resynthesis of GABA in neurons, has a positive effect on the bioeletric activity of the brain [4], acts as an antihypoxant and neuroprotective agent [5]. N.V. Tsygan et al. (2015) proved that the use of Cytoflavin lead to early and intensive activation of neurotrophic mechanisms in astrocytes, which contributes to neuroprotection in acute ischemic stroke [17]. The drug increases the brain's tolerance to ischemia, especially in patients over 65 [1].

According to V.V. Kovalchuk et al. (2014), Cytoflavin improves the recovery of neurological functions, normalizes the psychoemotional state, which improves the quality of life and social adaptation of patients after the stroke [18]. A multicenter, randomized clinical-instrumental prospective study conducted by S.A. Rumyantseva (2014) showed that the use of the drug in the acute period of stroke significantly improved the neurological status and functional outcome, especially in patients with a score of 18-20 points according to NIHSS. The treatment with Cytoflavin for 10 days in a daily dose of 20 ml resulted in a reduction of the ischemic area by 25%, and by 29% within 20 days [19, 20, 21]. Y.V. Karakulova et al. (2016) showed that the inclusion of Cytoflavin into the treatment of ischemic stroke (early recovery period) in a dose of 20 ml intravenous drop infusion once a day for 10 days, and then 2 tablets twice a day for a month increased the efficacy of treatment, which was manifested by significant positive dynamics of neurological symptoms and improvement of cognitive functions [22].

The efficacy of treatment for acute ischemic stroke after thrombolytic therapy with Cytoflavin is of a particular interest. I.E. Sazonov et al. (2016) observed the significant reduction in the severity of neurologic symptoms and a high percentage of successful outcomes on the 10^{th} day of treatment [23].

CEREBROLYSIN

Cerebrolysin is a complex of low molecular weight biologically active peptides derived from the pig's brain. The drug penetrates the blood-brain barrier directly to neurons, has an organ-specific multimodal effect on the brain, providing metabolic regulation, neuroprotection, functional neuromodulation and neurotrophic activity [4]. S.M. Hassanein et al. (2016) suggested that Cerebrolysin might be equivalent to stem cell therapy [24].

The meta-analysis carried out by S.L. Plavinsky (2016), demonstrated the efficacy of Cerebrolysin in ischemic stroke, with doses ranging from 10 ml per day to 50 ml per day, and duration from a week to 2 weeks, and a period of observation from a week to a year [25]. A prospective, blind, placebo-controlled experimental study in the ischemic stroke model demonstrated statistically significant differences in neurological outcomes depending on the dose of the drug. The use of Cerebrolysin in a dose of 2.5 ml/kg and more improved the functional outcome of the disease, and it reduced the volume of cerebral infarction at a dose of 5 ml/kg [26].

A randomized double-blind study conducted by L.X. Xue et al. (2016) found that in patients with acute ischemic stroke of moderate severity, who had been given Cerebrolysin intravenously for 10 days in the first 12 hours after the onset of the disease, neurological status and functional outcome improved on the 11th and 21st day after the onset of the stroke in comparison with the placebo group [27]. A large, randomized, double-blind, placebo-controlled, clinical trial of CASTA showed that administration of Cerebrolysin to patients in the first 12 hours from the onset of hemispheric stroke in a dose of 30 mL for 10 days resulted in better neurologic recovery and functional outcomes in patients with an NIHSS score greater than 12 upon admission to hospital [28]. A prospective, multicenter, randomized, double-blind, placebo-controlled, CARS study (2016) demonstrated that patients who received Cerebrolysin from 24 to 72 hours after the onset of stroke symptoms at a dose of 30 mL per day for 21 days, showed the improvement of motor function in the upper limbs on day 90 as compared with patients taking placebo [29]. A prospective, multicenter, randomized, double-blind, placebo-controlled study by W.H. Chang et al. (2016), showed that the prescription of Cerebrolysin in the first 7 days after the onset of stroke in patients with acute stroke and moderate or severe motor failure lead to significant regression of motor disorders in comparison with the placebo group [30]. V.N. Shishkova et al. (2015) conducted an open, randomized, controlled trial whivh showed the clinical efficacy of Cerebrolysin of 20 ml intravenously 5 days a week for 4 weeks, in addition to the standard course of neurorehabilitation measures in patients with aphasia of varying degrees associated with ischemic stroke [31] . However, in six large, randomized controlled clinical trials, there have been a greater trend in the efficacy of Cerebrolysin treatment [3, 28, 29, 32, 33, 34, 35].

A.Y. Kulikov et al. (2015), performed a pharmacoeconomic analysis of the treatment in patients with moderate and severe ischemic stroke (NIHSS 12 or more upon admission) and found that only Cerebrolysin had an evidence base for the treatment of moderate to severe ischemic stroke and this was "an advantageous product in terms of economic costs" [36].

A serious prospective, randomized, double-blind, placebo-controlled trial, performed by W. Lang et al., was devoted to the safety and efficacy of Cerebrolysin in combination with thrombolytic therapy (2013). Patients were given a drug in a dose of 30 ml for an hour after thrombolysis, and then daily at the same dose for 10 days. The authors noted a trend toward better recovery during the treatment, but no statistically significant differences were found [32].

CORTEXIN

Cortexin (cattle brain cortex polypeptides) is a water-soluble complex that penetrates the blood-brain barrier directly to neurons and has nootropic, neuroprotective, antioxidant and tissue-specific effects. The drug leads to activation of peptides of neurons and neurotrophic factors of the brain, optimizes the balance of metabolism of excitatory and inhibitory amino acids, dopamine, serotonin, has a GABAergic effect, reduces the level of paroxysmal convulsive activity of the brain and improves its bioelectrical activity, prevents the formation of free radicals (products of lipid peroxidation) [4].

The efficacy and safety of Cortexin in the complex treatment of patients with ischemic stroke in the acute and early recovery period was proved in a multicentre prospective, double-blind, placebo-controlled study conducted by V.M. Alifarova et al. (2014). The authors recommended intramuscular injections of the drug in a dose of 10 mg 3 times a day, by two courses of 10 days [37]. Somewhat later, the research data by L.V. Stakhovskaya et al. (2012) and L.A. Belova et al. (2016) were published, in which the treatment of patients with acute extensive hemispheric ischemic stroke was performed with Cortexin 10 mg intramuscularly twice a day for 10 days, with a repeat course of the same therapy 10 days later. The authors noted the most complete regression of the neurological deficit and improvement of the functional state during the acute and the entire early recovery period of ischemic stroke [38, 39], a better recovery of cognitive functions [38, 40], a faster and more complete return to normal quality of life than in patients, who received one course of Cortexin or only basic treatment [41].

The efficacy and safety of low doses of Cortexin has been demonstrated in an analytical review of 15 years of drug use [42]. So M.A. Evzelman et al. (2013) used the drug in an acute, early recovery and late recovery period for the treatment of ischemic stroke. The drug was administered in a dose of 10 mg once a day intramuscularly for 10 days in an acute period and at the same dose for 3, 6, 9 months of treatment. The authors revealed a regression of significant motor disorders, stabilization and restoration of cognitive functions, a decrease in the risk of post-stroke dementia development [43].

S.K. Zyryanov et al. (2012) proved the clinical and pharmacoeconomic reasonability of Cortexin in the acute and early recovery period of ischemic stroke and found that, from the point of view of cost-effectiveness, the most optimal strategy is two courses of 20 mg per day for 10 days [44].

CITICOLINE

Citicoline sodium (Ceraxon, Recognan, Quinel, Neipilept, etc.) is a precursor of key ultrastructural components of the cell membrane (mainly phospholipids) and has a wide spectrum of action: it helps to repair damaged cell membranes, inhibits the effect of phospholipases, preventing excessive formation of free radicals, and also prevents the death of cells, affecting the mechanisms of apoptosis. The use of the drug in the acute period of stroke

contributes to a decrease in the amount of damage to the brain tissue and improves the cholinergic transmission [4].

Protective effect of Citicoline was first described more than 30 years ago on the model of acute cerebral ischemia (Boismare F., 1978). Subsequently, numerous studies were conducted involving the use of the drug in treatment regimens at different times and at different doses. The results of the studies were ambiguous and interpreted with caution [45]. Therefore, the international multi-center prospective double-blind, randomized placebo-controlled study ICTUS was justified. The foundings were also ambiguous. On the one hand, the use of Citicoline in a dose of 2,000 mg per day for 6 weeks in the treatment of acute stroke of moderate severity, including patients after thrombolytic therapy, did not lead to a better recovery in comparison with the placebo group. On the other hand, it should be noted that almost half of the patients (47%) received thrombolytic therapy and the patients achieved the greatest possible recovery after administration of the recombinant tissue plasminogen activator, so the effect of metabolic therapy was not obvious. In a sub-study of ECCO 2000 Citicoline Trial-DWI, a comparison of primary magnetic resonance imaging and neuroimaging data at week 12 of Citicoline therapy (2,000 mg/day for six weeks) showed a significant decrease in cortical damage, which was associated with a better clinical outcome [46].

CHOLINE ALPHOSCERATE

Choline alphoscerate (Gliatilin, Cerepro, Cereton, etc.) is a precursor of choline, increases production and stimulates the release of acetylcholine from axon terminals. The drug improves feeling, mental activity, concentrates attention, memorization and the ability to reproduce the information obtained, optimizes cognitive and behavioral responses, eliminates emotional instability, apathy [4]. Choline alphoscerate is widely used in neurological practice, it is effective and safe [47].

M.M. Odinak et al. (2010) conducted a multicenter study on the efficacy of choline alphoscerate in the treatment of patients with acute ischemic stroke. Patients were prescribed choline alphoscerate for 3 months after the onset of stroke according to the schedule: 2,000 mg/day for 15 days, then 1,000 mg/day for 15 days, then 800 mg/day for 60 days. The authors found that the use of the drug significantly limited the growth of cerebral infarction from the first day of therapy [48]. O.I. Vinogradov et al. (2013) showed that the use of choline alfoscerate no later than 12 hours after the development of ischemic stroke at a dose of 1,000 mg per day intravenously for 10 days with the subsequent oral administration of the drug in the form of capsules of 400 mg 3 times a day for 20 days after the 30-day course of treatment led to significant regression of the severity of neurologic symptoms and achieved rehabilitation goals [49]. According to T.S. Mishchenko et al. (2016), the use of choline alfoscerate in patients in the recovery period of ischemic stroke at a dose of 1,000 mg once a day (total 14 days), and then 400 mg twice a day (total 2 months) reduced the severity of subjective and objective neurological symptoms. The improvement of impaired cognitive functions was noted in patients, including recovery of mental alertness and memory, improvement of mental and physical working capacity, emotional state of patients, which increased the effectiveness of rehabilitation measures [50, 51]. L. Onchul (2015) showed that the use of the drug reduced the level of disability, which resulted in better social rehabilitation of post-stroke patients [52]. F. Amenta et al. (2014) performed a double-blind study of ASCOMALVA and revealed regress of cognitive deficits in patients with ischemic stroke, who took a combination of choline alfoscerate and cholinesterase inhibitors. The combination of drugs allowed to prolong / increase the efficacy of cholinergic therapy in cognitive disorders associated with ischemic cerebrovascular injury [53].

ACTOVEGIN

Actovegin activates metabolism in tissues, improves trophism and stimulates regeneration. The drug consists of deproteinized extract of calf blood, which is obtained by dialysis and ultrafiltration. The mechanism of action is an antihypoxic, the drug positively affects the transport and utilization of glucose, enchances aerobic oxidation. Actovegin increases concentrations of ATP, ADP, phosphocreatine, amino acids (glutamate, aspartate) and GABA in the brain [4].

In a large randomized, double-blind, placebo-controlled ARTEMIDA trial, the efficacy and safety of the drug in patients with reduced cognitive function after stroke was proven. The inprovement of cognitive functions was noted in patients over 60 with the first acute cerebral infarction of hemispheric location with neurological deficiency NIHSS 3-18 and up to MoCA 25 after treatment with Actovegin. The drug was administered intravenously at a dose of 8 mg/ml in the form of a solution for injection (0.9% NaCl 250 ml/200 mg) for 20 days and then orally at a dose of 200 mg for six months. During the following 6 months, patients were treated according to standard clinical practice [54]. In the experiments on the model of ischemic stroke, it was demonstrated that therapy with Actovegin improved spatial perception and memory. Such a pharmacological effect was associated with hippocampal neuroprotection [55].

According to E.Z. Yakupova, Actovegin reduces the ten-year risk of stroke. The authors associated the efficacy of Actovegin to the effects on the central and peripheral structures of the autonomic nervous system, the hypotensive effect with humoral, metabolic and neurogenic effects on the vessel wall [56].

However, despite all the positive effects of Actovegin on general and cognitive recovery, its use in the acute phase of ischemic stroke does not significantly improve the neurological status of patients, as demonstrated in the study of V.I. Yershov (2011) [57].

THE CHOICE OF DRUGS FOR METABOLIC THERAPY OF ISCHEMIC STROKE

In pursuit of the best clinical effect in the treatment of cerebral infarction, doctors prescribe a large number of metabolic drugs. However, polypharmacy increases the risk of side effects. In this regard, the question reasonability and efficacy of using a combination of drugs from different pharmacological groups affecting brain metabolism is controversial. At present, there are no recommendations or guidelines for the use of metabolic therapy in the acute period of stroke. In order to avoid polypharmacy, doctors are always in creative search, which drug to choose and prescribe.

A.A. Skoromets and V.V. Kovalchuk conducted a study to assess the efficacy of drugs with nootropic, metabolic and antioxidant properties, as well as pathogenetic and symptomatic drugs, differentially used in ischemic stroke. The drugs were given as monotherapy in the course of the basic standard treatment during month 1,6 and 12 of the disease, and a year later the motor and speech functions, the level of household adaptation, were assessed. The most effective drugs were Actovegin and Choline alfoscerate [58]. On the other hand, in a large ARTEMIDA study, it has been proven that Actovegin did not affect the recovery of neurologic deficits, but only improved cognitive function [57, 54]. According to A.A. Skoromets and V.V. Kovalchuk, Cerebrolysin appeared in the group of drugs with an indifferent effect on recovery of functions in patients after a stroke, as there was no evidence of any effect on the increase in the number of patients with sufficient and complete recovery [58]. However, in V.I. Yershov demonstrated that the use of Cerebrolysin in a daily dosage of 10 ml for 10 days after the development of ischemic stroke leas to a greater regression of neurologic symptoms by the 21st day of the disease in comparison with patients who did not receive the drug. The author reported that a similar result was observed when Citicoline was included in the daily regimen of 2 g for 10 days [57].

The reasonability of prescribing a complex of drugs consisting of several metabolic drugs of different pharmacological groups is relevant. Perhaps, to achieve the best result, it is necessary not to choose between antihypoxants and neuroprotectors, but use the combination. So, in the study G.I. Izhbuldina the use of a combination of metabolic drugs ethyl methyl hydroxypyridine succinate (at a dose of 500.0 mg intravenously for the first 10 days) and Cerebrolysin (1.0 ml intramuscular for 10 days) in addition to the main stroke treatment improved the lipid spectrum, reduced the intensity of free radical oxidation lipids, stabilized the parameters of hemostasis. The combined treatment was accompanied by an increase in survival rate and a rapid regression of the neurological deficit [59]. According to E.B. Kuznetsova, patients with the consequences of ischemic stroke who received a combination of ethyl methyl hydroxypyridine succinate (5 ml of a 5% solution intravenously for 15 days) and Cortexin (10 mg per day intramuscularly) showed a regress of neurological deficit, significantly improved cognitive and emotional status and increased quality of life and rehabilitation potential [60].

In the study of I.I. Kukhtevich, in patients with acute ischemic stroke of moderate severity (NIHSS 7-14), combined metabolic therapy including ethyl methyl hydroxypyridine succinate (250 mg per day), Cytoflavin (10 ml per day), Choline Alfoscerate (1,000 mg per day) and Actovegin (200 mg per day) for 15 days showed positive dynamics of the neurological status by the 21st day of the disease, as well as a lower dependence on others in everyday life than in patients who received only ethyl methyl hydroxypyridine succinate [61]. It remains an undecided issue, which particular drug achieved the best clinical effect in this study and whether prescribing several drugs of one pharmacological group at a time is reasonable.

THE SAFETY OF NEUROPROTECTIVE THERAPY

Despite the optimistic view of the researchers concerning the metabolic therapy, there is always concern not only about its efficacy, but also safety. It was suggested that some of tested drugs could inhibit not only the mechanisms of nerve damage in stroke, but also activation of recovery processes [62].

In 1996, pharmaceuticals, allografts and even food additives from cattle tissues were banned from manufacturing and using throughout Switzerland. In 2011, in Canada and the United States of America, this ban was followed by the publication of the results of a 15-year study (1996-2010), in which the countries of the world were divided on the use of the drug Actovegin. It was revealed that in the countries where Actovegin was used, the total frequency of all dementia cases was one-third (1.3:1) higher than in countries where Actovegin was never used. It is known that cattle suffer from prion spongiform encephalopathy "mad cow disease", to which man is also susceptible (Creutzfeldt-Jakob disease). Germany and Austria are countries with a high prevalence of mad cow disease, and Actovegin is made from the blood of Austrian and German calves. In Russia and Belarus, imported (mainly German and Austrian) raw materials (brain of slaughter cattle), Cortexin is mainly produced. Cerebrolysin is produced in Russia as well, but it is made from pig brains, where prion diseases have not been identified. Under current legislation of Russia and Belarus, drugs are not tested for prion infections either as a food product or as a raw material for pharmaceutical production [63].

Thus, when prescribing a medication to a patient that is not included in the recommendations of modern guidelines for the treatment of ischemic stroke, it is always worthwhile to correlate the use of the medicine and the possible risk. Each drug is primarily a foreign chemical formula with possible unintended effects.

In conclusion, it should be noted that despite a large number of publications, metabolic therapy of ischemic stroke is an issue that requires further large independent clinical studies.

REFERENCES

1. Anatskaya L.N. A cerebral infarction in elderly patients. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2011; (8–2: Stroke): 74–80. (In Russian).
2. Kulikov A., Abdrashitova G. Budget Impact Analysis of Cerebrolysin In The Treatment of Acute Ischemic Stroke of Moderate and Severe Degrees of Severity In The Russian Federation. *Value Health*. 2015; 18 (7): A699. PMID: 26533918. DOI: 10.1016/j.jval.2015.09.2612.
3. Ziganshina LE, Abakumova T, Vernay L. Cerebrolysin for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2016; 12: CD007026. PMID: 27918088. DOI: 10.1002/14651858.CD007026.pub4.
4. *Handbook of Vidal. Medicinal preparations in Russia – 2017*. Moscow: Vidal' Rus Publ., 2017. 1240 p. (In Russian).
5. Yasnetsov V.V., Prosvirova E.P., Tsublova E.G., et al. Comparative studies of antihypoxic, neuroprotective and analgesic action of succinate-containing drugs. *Aviakosmicheskaya i ekologicheskaya meditsina*. 2012; 46 (6):41–45. (In Russian).
6. Odinak M.M., Yanishevskiy S.N., Tsygan N.V., et al. The use of succinates for the correction of metabolic disorders in the penumbra in patients with stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2013; 113(12–2: Stroke): 55–60. (In Russian).
7. Skvortsova V.I., Stakhovskaya L.V., Nartsissov Ya.R., et al. Randomized double blind placebo-controlled study of Mexidol efficacy and safety in the treatment of ischemic stroke in the acute period. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2006; (18–2: Stroke): 47–54. (In Russian).
8. Seregin V.I., Dronova T.V. The use of mexidol in the intensive treatment of acute severe ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2015; 115 (3–2: Stroke): 85–87. (In Russian).
9. Androfagina O.V., Kuznetsova T.V., Svetkina A.A. Mexidol in the rehabilitation of patients in the acute ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2015; 115 (12–2: Stroke): 77–79. (In Russian).
10. Kispaeva T.T. Preventive/therapeutic correction of the development and progression of cognitive deficit in patients after stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2013; 113(7): 76–79. (In Russian).
11. Novikova L.B., Sharafutdinova L.R., Sharapova K.M. The use of mexidol in acute period of ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2013; 113 (9): 83–85. (In Russian).
12. Lutskiy M.A. Efficacy of Mexidol in complex treatment of patients with ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2010; 110 (4–2: Stroke): 57–59. (In Russian).
13. Kurushina O.V., Barulin A.E., Konovalova O.V. Correction of psychoemotional and autonomic dysfunction in patients with ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2013; 113 (9–2: Stroke 2): 50–54. (In Russian).
14. Shchepankevich L.A., Nikolaev Yu.A., Dolgova N.A., Chipova D.T. Optimization of hypolipidemic therapy in patients with ischemic stroke and diabetes mellitus. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2016; 116(2): 42–45. (In Russian).
15. Koval'chuk V.V. Neurometabolic therapy in secondary prevention of stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014; 114(3): 24–28. (In Russian).
16. Chefranova Zh.Yu., Makotrova T.A., Udachin V.A., Koledintseva E.V. Efficacy of mexidol in the combination with thrombolytic therapy in patients with ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2012; 112(4): 49–52. (In Russian).
17. Tsygan N.V., Trashkov A.P., Yakovleva V.A., et al. Characteristics of the regulation of neurotrophic mechanisms in ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2015; 115(7): 112–116. (In Russian).
18. Koval'chuk V.V, Khafizova T.L., Galkin A.S. The use of neurometabolic treatment in the complex rehabilitation in poststroke patients. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014; (11–1): 61–66. (In Russian).
19. Rumyantseva S.A., Silina E.V., Tsukurova L.A., et al. Modern methods of energy homeostasis correction in elderly patients. *Uspekhi gerontologii*. 2014; 27(4): 746–752. (In Russian).
20. Rumyantseva S.A., Silina E.V., Chichanovskaya L.V., et al. Efficacy of antioxidant energocorrection in brain infarction (results of a multicenter randomized trial). *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014; 114(10): 49–55. (In Russian).
21. Chichanovskaya L.V., Tsukurova L.A., Kovalenko A.L., et al. Performance evaluation of integrated cytoprotective therapy of different duration in patients with cerebral infarction. *Eksperimental'naya i klinicheskaya farmakologiya*. 2015; 78(1): 21–26. (In Russian).
22. Karakulova Yu.V., Selyanina N.V., Zhelnin A.V., et al. Effect of antioxidant therapy on neurotrophins and processes of rehabilitation after stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2016; 116(8): 36–39. (In Russian).
23. Sazonov I.E., Lavrent'eva I.V., Golovina N.P. The use of cytoflavin in reperfusion in ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2016; 116(3): 25–28. (In Russian).
24. Hassanein S.M., Deifalla S.M., El-Houssinie M., Mokbel S.A. Safety and Efficacy of Cerebrolysin in Infants with Communication Defects due to Severe Perinatal Brain Insult: A Randomized Controlled Clinical Trial. *J Clin Neurol*. 2016; 12(1): 79–84. PMID: 26365023. DOI: 10.3988/jcn.2016.12.1.79.
25. Plavinskiy S.L., Shabalkin P.I. A meta-analysis.Cerebrolisyn, Cortexin, Cellex, efficiency in vascular dementia, Alzheimer''s disease and ischemic stroke. *Meditsina*. 2016; (2). Available at: http://fsmj.ru/015231.html (Accessed 28 February 2018) (In Russian).
26. Zhang L., Chopp M., Lu M., et al. Cerebrolysin dose-dependently improves neurological outcome in rats after acute stroke: A prospective, randomized, blinded, and placebo-controlled study. *Int J Stroke*. 2016; 11(3): 347–355. PMID: 26763925. DOI: 10.1177/1747493015625645.
27. Xue L.X., Zhang T., Zhao Y.W., et al. Efficacy and safety comparison of DL-3-n-butylphthalide and Cerebrolysin: Effects on neurological and behavioral outcomes in acute ischemic stroke. *Exp Ther Med*. 2016; 11(5): 2015–2020. PMID: 27168844. DOI:10.3892/etm.2016.3139.
28. Heiss W.D., Brainin M., Bornstein N.M. et al. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. *Stroke*. 2012; 43(3): 630–636. DOI: 10.1161/STROKEAHA.111.628537.
29. Muresanu D.F., Heiss W.D., Hoemberg V., et al. Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial. *Stroke*. 2016; 47(1): 151–159. PMID: 26564102. DOI: 10.1161/STROKEAHA.115.009416.
30. Chang W.H., Park C.H., Kim D.Y., et al. Cerebrolysin combined with rehabilitation promotes motor recovery in patients with severe motor impairment after stroke. *BMC Neurol*. 2016; 16: 31. PMID: 26934986. DOI: 10.1186/s12883-016-0553-z.
31. Shishkova V.N., Zotova L.I., Malyukova N.G., et al. An assessment of cerebrolysin effect on BDNF level in patients with post stroke aphasia depending on carbohydrate metabolism disorders. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2015; 115(5–1): 57–63. (In Russian).
32. Lang W., Stadler C.H., Poljakovic Z., et al. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and Cerebrolysin in acute ischaemic hemispheric stroke. *Int J Stroke*. 2013; 8(2): 95–104. PMID: 23009193. DOI: 10.1111/j.1747-4949.2012.00901.x.
33. Nazari S., Mazdeh M., Taheri M., et al. A double-blind, placebo-controlled and randomized trial of Cerebrolysin in patients with acute ischemic stroke in Iran. *Glob Adv Res J Med Med Sci*. 2015; 4(5): 235–239.
34. Chukanova E.I., Gusev E.I., Belousov D.Yu., et al. Results of multicenter randomized controlled clinical and economic study of acute ischemic stroke therapy with Cerebrolysin. *Kachestvennaya klinicheskaya praktika*. 2011; (3): 14–37. (In Russian).
35. Amiri-Nikpour M.R., Nazarbaghi S., Ahmadi-Salmasi B., et al. Cerebrolysin effects on neurological outcomes and cerebral blood flow in acute ischemic stroke. *Neuropsychiatr Dis Treat*. 2014; (10): 2299–2306. PMID: 25516711. PMCID: PMC4263193 DOI: 10.2147/NDT.S75304.
36. Kulikov A.Yu., Abdrashitova G.T. Pharmacoeconomic analysis of treatment of patients with severe and moderate ischemic stroke (NIHSS Score > 12). *Farmakoekonomika: Teoriya i praktika*. 2015; 3(4): 30–40. (In Russian).
37. Alifirova V.M., Dadashev M.N., Doronin B.M. et al. Clinical efficacy and pharmacoeconomic characteristics of the neuroprotection with low doses of cortexin in the treatment of acute ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014; 114(4): 41–46. (In Russian).
38. Stakhovskaya L.V., Meshkova K.S., Dadasheva M.N., et al. Results of multicenter randomize prospective double-blind placebo-controlled study of the safety and efficacy of cortexin in acute and subacute periods of hemispheric ischemic stroke. *Vestnik Rossiyskoy Voenno-meditsinskoy akademii*. 2012; 1(37): 238–244. (In Russian).

39. Belova L.A., Mashin V.V., Abramova V.V., et al. Efficacy of cortexin in acute and recovery periodes of hemispheric ischemic stroke. Zh Nevrol Psikhiatr Im S S Korsakova. 2016; 116(10): 38–42. (In Russian)
40. Belova L.A., Mashin V.V., Abramova V.V., et al. Cognitive impairment in patients poluchennym ischemic stroke in the acute and early recovery periods in the process of neuroprotection low-dose drug cortexin. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2016; 116(8–2: Stroke): 40–43. DOI: 10.17116/jnevro20161168240-43 (In Russian).
41. Belova L.A., Mashin V.V., Abramova V.V., et al. Effect of cortexin on the quality of life in the early rehabilitative period after hemispheric ischemic stroke. *Klinicheskaya meditsina*. 2016; 94(2):138–143. (In Russian).
42. D'yakonov M.M., Shabanov P.D. Long-term experience of low-dose peptide neuroprotection in medicine. *Vestnik Kazakhskogo Natsional'nogo meditsinskogo universiteta*. 2015; (2): 371–373. (In Russian).
43. Evzel'man M.A., Aleksandrova N.A. Cognitive disorders and their correction in patients with ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2013; 113 (10): 36–39. (In Russian).
44. Zyryanov S.K., Stakhovskaya L.V., Gil'deeva G.N., Meshkova K.S. Clinical and economical analysis of effectiveness of cortexin in patients with hemispheric ischemic stroke in acute and early recovery period in specialized vascular centers. *Vestnik Rossiyskoy Voenno-meditsinskoy akademii*. 2012; (3): 69–74. (In Russian).
45. Yavorskaya V.A., Flomin Yu.V., Grebenyuk A.V. Citicoline at Acute stroke: Mechanism of Action, Safety and Effectiveness (Scientific Review). *Mezhdunarodnyy nevrologicheskiy zhurnal.* 2011; 2: 98–104. (In Russian).
46. Álvarez-Sabín J., Román G.C. The Role of Citicoline in Neuroprotection and Neurorepair in Ischemic Stroke. *Brain Sci*. 2013; 3(3): 1395–1414. PMID: 24961534. PMCID: PMC4061873. DOI: 10.3390/brainsci3031395.
47. Starchina Yu.A. Use of cereton in neurological care. *Nevrologiya, neyropsikhiatriya, psikhosomatika*. 2011; (2): 81–85. (In Russian).
48. Odinak M.M., Voznyuk I.A., Piradov M.A., et al. Multicentral pilot clinical trial of gliatilin in treatment of acute ischemic stroke. *Annaly klinicheskoy i eksperimental'noy nevrologii*. 2010; (1): 20–28. (In Russian).
49. Vinogradov O.I., Daminov V.D., Rybalko N.V. The use of choline alfoscerate (gliatiline) in patients with ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2013; 113(1): 43–45. (In Russian).
50. Mishchenko T.S., Mishchenko V.N., Lapshina I.A. Gliatilin in the Treatment of Post-Stroke Patients. *Mezhdunarodnyy nevrologicheskiy zhurnal*. 2016; 4(82): 25–31. (In Russian).
51. Mishchenko V.N., Lapshina I.A. Gliatilin in Treatment of Patients in the Recovery Period of Cerebral Stroke. *Mezhdunarodnyy nevrologicheskiy zhurnal*. 2011; 5(43): 101–108. (In Russian).
52. Onchul L. Gliatilin: a modern view on the problem of cholinergic therapy in the treatment of ischemic stroke. *Meditsina neotlozhnykh sostoyaniy*. 2015; 7(70): 53–55. (In Russian).
53. Amenta F., Carotenuto A., Fasanaro A.M., et al. The ASCOMALVA (Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease) Trial: interim results after two years of treatment. *J Alzheimers Dis*. 2014; 42 (Suppl 3): S281–288. PMID: 24898643. DOI: 10.3233/JAD-140150.
54. Guekht A., Skoog I., Edmundson S., et al. ARTEMIDA Trial (A Randomized Trial of Efficacy, 12 Months International Double-Blind Actovegin): A Randomized Controlled Trial to Assess the Efficacy of Actovegin in Poststroke Cognitive Impairment. *Stroke*. 2017; 48: 1262–1270. PMID: 28432265. PMCID: PMC5404405. DOI: 10.1161/STROKEAHA.116.014321.
55. Meilin S., Machicao F., Elmlinger M. Treatment with Actovegin improves spatial learning and memory in rats following transient forebrain ischaemia. *J Cell Mol Med*. 2014; 18(8): 1623–1630. PMID: 24797227. PMCID: PMC4190908. DOI: 10.1111/jcmm.12297.
56. Yakupov E.Z., Nalbat A.V. The measures of autonomic homeostasis as predictors of an individual risk of stroke and their dynamics during therapy with Actovegin. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2015; 115 (10-2: To help a practical doctor): 31–42. DOI: 10.17116/jnevro201511510231-42 (In Russian).
57. Ershov V.I. Comparative aspects of using neuroprotectors in the management of patients with ischemic stroke. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2011; 111 (8–2: Stroke): 41–44. PMID: 22224244.
58. Skoromets A.A., Koval'chuk V.V. Drug Rehabilitation in Stroke Patients. *Mezhdunarodnyy nevrologicheskiy zhurnal*. 2007. 2(12): 9–12. (In Russian).
59. Izhbul'dina G.I. Changes in the hemostasis system and free-radical lipid oxidation in the acute stage of ischemic stroke in patients on neuroprotection treatment. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2012; 112 (3–2: Stroke): 31–37. (In Russian).
60. Kuznetsova E.B., Salina E.A., Sholomov I.I. The possibility of treatment of cognitive impairment in the complex therapy of patients with the consequences of cerebral infarction. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2015; 115 (11): 103–106. (In Russian).
61. Kukhtevich I.I., Aleshina N.I., Levashova O.A. The active neuroprotective therapy of acute carotid ischemic stroke of moderate severity. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014; 114 (12–2: Stroke): 38–42. (In Russian).
62. Lo E.H. A new penumbra: transitioning from injury into repair after stroke. *Nat Med*. 2008; 14(5): 497–500. PMID: 18463660. DOI: 10.1038/nm1735.
63. Pavlov I.E. Caution: Actovegin, Solcoseryl, Cortexin, Cerebrosolate! 2012. Avalable at: http://www.medkrug.ru/blog/display_entry/54283. (Accessed 28 February 2018). (In Russian).

Received on 04.09.2017
Accepted on 26.01.2018