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Antioxidant Treatment of Ischemic Brain Lesions

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Acute and chronic brain lesions, especially cerebral stroke, have become the leading causes of death and disability in the Russian population, which is a major argument for developing effective methods for pathogenetic treatment [1–4]. Therapeutic strategies based on the principle of energy correction are regarded as highly effective methods of neuroprotection. These strategies allow cell energetics to be balanced, decreasing the extent of cerebral impairments at the first stages of the "ischemic cascade," where decreases in ATP synthesis and the progression of oxidative stress act as catalysts [5–9].

ATP synthesis in the oxidative phosphorylation cycle is a multistep process, as each round of the cycle produces several ATP molecules via the splitting, transformation, and decarboxylation of oxidation substrates. One of the most important steps in the cycle, given the greatest energy yield, is the oxidation of succinic acid. Activation of the oxidation of succinic acid and its salts – succinate – significantly increases ATP synthesis, preventing the development of severe consequences of energy deficiency both for cells and tissues and for the body as a whole. With its catalytic action on the Krebs cycle, succinic acid decreases the blood concentrations of other products of this cycle – lactate, pyruvate, and citrate, which accumulate rapidly at different stages of hypoxia. The adaptogenic importance of succinic acid oxidation by succinate dehydrogenase is the phenomenon of rapid ATP resynthesis. The role of succinic acid in the adequate functioning of the nervous system is particularly important. The gamma-aminobutyrate shunt (Roberts cycle), in which succinic acid, an active stimulator of ATP synthesis, is repeatedly resynthesized from gamma-aminobutyric acid (GABA) via an intermediate succinic aldehyde stage, operates in nervous tissue [1, 8, 10, 11]. In conditions of oxidative stress, succinic acid can also be formed by the oxidative deamination of α-ketoglutaric acid in the liver. The antioxidant activity of succinic acid also arises as a result of its influence on the transport of transmitter amino acids, normalization of histamine and serotonin content, and increases in the microcirculation in the organs and tissues. The anti-ischemic effect of succinic acid is associated not only with activation of oxidation by succinate dehydrogenase, but also with restoration of the activity of the key oxidative-reductive enzyme in the mitochondrial respiratory chain – cytochrome oxidase [1, 11, 12].

One of the most effective and widely used pharmacological energy correctors synthesized from a succinic acid salt is Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate), a semisynthetic antioxidant. With a wide spectrum of action on different cell metabolism-regulating mechanisms, along with antioxidant, free radical-inhibiting, and membrane-protecting activities, this agent decreases the activation of lipid peroxidation and increases the activity of the physiological antioxidant system [12–14]. Mexidol activates mitochondrial energy-synthesizing functions, improving cell energy metabolism. The agent also stabilizes lipid homeostasis and decreases cholesterol and low density lipoprotein levels [10], has membrane-stabilizing actions and modulatory influences on membrane-bound enzymes, neurotransmitter transporter ion channels, and receptor complexes, including benzodiazepine, GABA, and acetylcholine receptors, and improves synaptic transmission, thus interacting with a variety of cerebral structures [10, 14, 15].

Improving and stabilizing brain metabolism, Mexidol also corrects microcirculation disorders, improves blood rheology, inhibits platelet aggregation, improves the func-

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tioning of the immune system, and activates intracellular protein and nucleic acid synthesis, resulting in stimulation of repair processes; it limits the size of the ischemic damage zone in hemispheric stroke. Patients with hemispheric lesions often show hyperoxia by the end of the first day of illness, due to hyperventilation syndrome. Patients have significant reductions in the concentrations of antioxidant system components [9, 16–19].

Intravenous infusions of Mexidol at doses of 100–1000 mg/day have marked antioxidant effects. The clinical efficacy of Mexidol consists of regression of general cerebral impairments (including impairments of consciousness), significant acceleration of the recovery of motor functions as compared with placebo, and decreases in the signs of vasomotor instability [9, 17, 20]. The overall membranotropic and antihypoxic actions of Mexidol allow it to be prescribed in the complex treatment of acute ischemia and hypoxia syndromes occurring in the diverse clinical situations, especially in ischemic and hemorrhagic cerebrovascular accidents. The efficacy of Mexidol has been demonstrated in both ischemic and hemorrhagic stroke. Studies showed that this agent should be used at appropriate doses: 800 mg/day by i.v. infusion for 14–15 days. Administration of Mexidol in the form of bolus i.v. doses of 100–300 mg as acute pharmacological tests in ischemic stroke improved the functional activity of the brain in terms of EEG data [19, 21]. These effects are obtained with agents with rapid onset of action, such that Mexidol can be used at the prehospital stage. Mexidol is currently used at doses of 200–400 mg in standard medical practice in patients with stroke at the prehospital stage, allowing patients' status to be stabilized in the acute period [8].

Some of the pharmacokinetic parameters of Mexidol, such as the C_{max} of 0.58 h from the moment of administration and the half-elimination time $T_{0.5}$ of 4 h [12, 14], allow the prescription regime to be adjusted for different clinical situations. In acute ischemic stroke, Mexidol is given at a dose of 300 mg twice daily with 12-h intervals on the basis of its pharmacokinetic properties (i.v. infusions diluted in physiological saline); the daily dose of Mexidol of 600 mg is recommended to continue for five days [16]. The dose is then decreased to 200 mg twice daily i.v. (400 mg/day) for the next 6–8 days. The agent is then given i.m. at single doses of 100 mg/day for the next two weeks, which is followed by transfer to prolonged use of oral formulations at doses of 125 mg 2–3 times daily. Oral courses last at least two months. Mexidol prescribed according to this protocol produces more marked improvements in neurological status than seen in patients receiving Mexidol by the standard scheme – 300 mg once daily for 10 days. This Mexidol protocol not only provides complete realization of the antioxidant and energy-correcting properties of the agent, but also gradual activation and "training" of the body's intrinsic antioxidant systems, as is evidenced by increases in their activity detected in laboratory tests [8, 16].

In particularly severe clinical situations, the effect of Mexidol used alone at standard doses may be inadequate for complete correction of oxidative stress. Considering the low toxicity of the agent, the Mexidol dose in these cases can be increased to 800–1000 mg/day [8, 17, 22, 23].

Because of its membrane-protective action, Mexidol decreases cell membrane viscosity and alters the binding of membranes with receptors and integral proteins. The agent acts on a variety of receptor systems, increasing the binding of transport proteins to GABAergic and benzodiazepine receptors [8, 14, 24]. This multi-receptor influence explains the multifactorial nature of the actions of Mexidol. Voronina [14] suggested that Mexidol induces allosteric (additional) changes in the conformations of many receptors, leading to improvements in ligand-receptor interactions, particularly in metabotropic receptors "working" through specific transport G-proteins. These actions are associated with the fact that the agent has additional effects, widening the sphere of its clinical applications to include anxiolytic and antiamnestic actions.

The anxiolytic properties of Mexidol, which are comparable with the effects of classical benzodiazepines [14, 24–27], are due to its marked $GABA_A$-modulating action. This clinical-pharmacological effect can be used in various ways, including: in agitated patients with acute stroke, Mexidol can be used alone; in situations where there is a need to enhance the actions of standard anxiolytics, Mexidol can be used in combination with other GABA-mimetics. The use of combined therapy should take cognizance of the fact that $GABA_A$ blockers (such as cephalosporins) can decrease the efficacy of Mexidol [8].

The antioxidant activity of Mexidol and its anxiolytic and, when the dose is increased to 750–1000 mg, sedative properties allow it to be used widely in the treatment of craniocerebral trauma (CCT), including during the acute phase of moderate and severe brain injury. At 8–12 days from the start of Mexidol treatment at a dose of 400 mg by i.v. infusion, improvements are seen in 80% of CCT patients. In patients with the long-term sequelae of closed CCT, prolonged use of Mexidol as a component of complex therapy produces decreases in the frequency of episodes of increased intracranial pressure, which usually occur after even mild CCT [6, 8, 14].

The synergism of Mexidol with antiepileptic agents (AEA) allows it to be used in combination with valproates, lamotrigine, and other AEA in the treatment of pharmacologically resistant epilepsy [8]. In particular, the combination of Mexidol with carbamazepine allows the dose of anticonvulsant to be decreased two-fold without any reduction in its therapeutic effect.

Combination with dopaminomimetics (Pronoran) allows Mexidol to be used as a component in the treatment of Parkinson's disease, vascular parkinsonism, and several other neurodegenerative diseases. Many studies have demonstrated that the antioxidant action of Mexidol appears more quickly than those of other agents [26, 28, 29].

The wide use of Mexidol in the treatment of acute stroke and chronic cerebral ischemia was started in the 1990s with studies in Fedin's clinic and at the Research Institute of Neurology, Russian Academy of Medical Sciences (now the Neurology Scientific Center). These studies demonstrated the clinical efficacy of this agent, with improvements in the state of brain electrogenesis, significant decreases in the activity of the oxidant system and simultaneous stimulation of the antioxidant systems in terms of parameters such as malondialdehyde, superoxide dismutase, etc. levels [18, 19]. Later studies, reported by Vinichuk, yielded analogous data [10]. Case–control studies showed that complex therapy including Mexidol significantly increased the level of regression of neurological deficit in stroke, decreasing the level of disability on a modified Rankin scale. Mexidol decreased the level of primary (diene conjugates) and secondary (malondialdehyde) products of lipid peroxidation and increased the activity of the enzymatic antioxidant defense system.

Double-blind, placebo-controlled studies reported by Skvortsova et al. [9, 17] demonstrated that early (during the first 6 h of onset of clinical symptoms of stroke) i.v. administration of Mexidol at a dose of 300 mg/day for 14 days led to significantly more marked regression of focal neurological symptomatology and improved outcomes from stroke. These studies also showed improvements in measures of brain bioelectrical activity on EEG traces and in parameters of the oxidative phosphorylation cycle, evidencing optimization of the operation of the mitochondrial respiratory chain.

A number of reports have addressed an interesting aspect of the actions of Mexidol as a component of complex treatment in combination with antihypertensives in patients with arterial hypertension and cardiac failure. The use of Mexidol was shown to produce not only stabilization of measures of psychoneurological status, but also significant improvements in measures of systemic hemodynamics and blood rheological properties [14, 16, 23, 30].

Studies reported by Kuznetsova [25] reflected the positive effects of combined treatment with Mexidol (i.v. infusions at a dose of 200 mg/day for seven days followed by tablets at a dose of 125 mg twice daily for two weeks) on the course of the recovery period in cerebral stroke. Mexidol treatment improved wellbeing, memory, and intellectual-mnestic functions. Courses of treatment with Mexidol in patients produced significant reductions in signs due to circulatory insufficiency in the vertebrobasilar basin (unsteady gait, vertigo), as well as headache, which to some extent is due to chronic hypoxia. Improvements were also seen in relation to the autonomic nervous system, and patients became less dependent on weather changes and stress. Treatment was followed by decreases in irritability and improvements in sleep, memory, and mood; patients had lower levels of depression on the Hamilton Geriatric Scale. There were also improvements in cerebral hemodynamics, with decreases in the thickness of the intima-media complex, and increases in linear systolic blood flow rate in the vessels of the carotid and vertebrobasilar basins.

Analogous results have also been obtained in other studies [14, 22]. The use of Mexidol produced significant improvements in the quality of life not only of stroke patients themselves, but also of their relatives, as patients experienced significant increases in levels of social adaptation and self-care skills, for example, the ability to use the toilet, wash, and eat independently.

Mexidol is also widely used in surgical practice, particularly for protection of the brain in patients undergoing vascular surgical interventions. Thus, a study of 272 patients showed that the use of Mexidol in the pre- and post-operative periods in the vascular surgical treatment of ischemic brain circulatory lesions increased safety and efficacy [31].

Finally, we note that pharmacoeconomic studies have demonstrated the efficacy of including Mexidol in the treatment of stroke, decreasing neurological deficit, reducing treatment duration, and increasing patients' quality of life. The economic effect of using Mexidol was 1.7–2.3 times greater than its acquisition cost [32].

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