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EFFICACY OF IPIDACRINE IN THE RECOVERY PERIOD OF ISCHAEMIC STROKE

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Abstract:

Vascular diseases of the brain continue to be a major medical and social problem. According to WHO, approximately 5 million people die each year from cerebrovascular diseases. About 80% of people who suffer a stroke become disabled, 10% of whom become severely disabled and require ongoing care. Only 10% of strokes end in full recovery within the first weeks of illness [3,4].

Keywords: Ischaemic Stroke, Recovery Period, Ipidacrine

INTRODUCTION:

Lesions of the peripheral nervous system are caused by a broad group of diseases, heterogeneous in their pathogenic mechanisms and clinical manifestations . Their most common clinical manifestations are peripheral paresis and pain syndromes. Similar clinical manifestations and the commonality of a number of underlying pathogenetic mechanisms enable the use of drugs that have a pronounced effect on the key links of the pathological process. One of the areas of treatment of these patients is the use of acetylcholinesterase inhibitors (AChE). Their prescription in peripheral nerve damage leads to an increase in the content of acetylcholine in the synaptic cleft, thereby providing activation of neuromuscular transmission and improving impulse conduction along the peripheral nerves. One representative of this class of drugs is Axamon (ipidacrine), which has a stimulating effect on neuromuscular transmission and excitation along the nerve fibres due to inhibition of AChE activity and blockade of potassium channels [2], which causes prolongation of the excitation period in presynaptic fibres during nerve impulse passage and provides a large amount of acetylcholine into the synaptic gap. It is believed that it is due to the selective blockade of membrane potassium channels (the key mechanism of action of the drug) and a simultaneous increase in the rate of calcium ions entry into axon terminations that prolongs the excitation period in the presynaptic fiber during nerve impulse passage, resulting in an increase in acetylcholine entry into the synaptic cleft [3]. The anticholinesterase effect of ipidacrine has been found to be short-lived (20-30 min) and reversible, whereas the blockade of potassium membrane permeability persists for 2 hours after administration. Clinical effects of ipidacrine recorded in experimental and clinical studies are confirmed by the results of electroneuromyography (ENMG). Thus, it has been shown that the use of ipidacrine in patients with peripheral paresis of various etiologies increased the amplitude of the M response in the affected muscles, increased amplitude and duration of motor unit potentials, decreased residual latency, characterizing the state of motor axon endings, which was evidence of activation of reinnervation processes [4]. A decrease in the duration of the residual latency reflects the recovery of the trophic supply and functional state of the axons and is a favourable prognostic sign with regard to recovery. It has also been found that prolonged use of ipidacrine increases the rate of propagation of excitation along the peripheral nerves, reflecting the activity of remyelination processes [5].

Due to the inhibition of sodium channel activity, the use of the drug provides a moderately pronounced anti-pain effect. This is supported by the fact that the blockade of potential-dependent sodium channels underlies the anti-pain action of some modern antiepileptic drugs [6]. There is also evidence to suggest that ipidacrine increases the duration of presynaptic membrane repolarisation and promotes the blockade of ectopic foci and ephaptic excitation transmission that are associated with the formation of neuropathic pain syndrome and crimpies . The anti-pain effect of ipidacrine is relatively less pronounced than the increase in neuromuscular transmission activity. However, it should be noted that the effect of the drug on the nature and severity of pain syndrome remains poorly understood. Further studies are required on its predominant effect on the nociceptive and neuropathic components of pain, determination of dose dependence of the therapeutic effect, and the ability to potentiate the effect of other drugs used for pain relief. In addition, ipidacrine has the properties of

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a partial agonist of M2-cholinergic receptors, the presence of which is associated with the ability of the drug to influence the processes of neuroplasticity [7]. This process is predominantly expressed in the tissue of central nervous system that allows using ipidacrine for treating patients with cerebrovascular, neurodegenerative diseases, the consequences of traumatic brain injury [8, 9]. It can be assumed that the positive effects of Axamon in patients with peripheral nervous system lesions can to some extent be realized through the effect on the central compensation mechanisms of the impaired functions.

CLINICAL EFFICACY OF IPIDACRINE

To date, there is considerable experience in clinical application of ipidacrine in various diseases of the peripheral nervous system. The efficacy of the drug in mono- and polyneuropathies with predominantly motor disorders - peripheral paresis - has been most extensively studied. The interest in the possibility of using ipidacrine in this contingent of patients was largely due to the relatively small number of drugs capable of affecting neuromuscular transmission with satisfactory tolerability. It should also be noted that determining the point of application of anticholinesterase drugs in peripheral nerve lesions is often difficult, given that the lesion area is located in the neuron body or axon, and the effects of drugs are realized mainly by increasing the concentration of the neurotransmitter acetylcholine in the synaptic gap. In this regard, the possibility of using ipidacrine is of extreme interest, given its direct effect not only on synaptic transmission processes, but also on impulse conduction along the nerve fibre [10, 11]. The results of an open clinical trial to assess the efficacy and tolerability of Axamon in patients with mononeuropathy are of considerable interest [12]. The study included 35 patients with peripheral nerve damage due to tunnel syndrome or cervical and/or lumbosacral radiculopathy due to an intervertebral disc herniation. The clinical diagnosis of polyneuropathy was confirmed by electromyography and ENMG. Patients in the main group received Axamon along with basic therapy (B-group vitamins, thioctic acid) for 2 weeks at 15 mg/ml per day (intramuscularly or subcutaneously), then at 20 mg 3 times a day for 4 weeks orally. Patients in the comparison group received only baseline therapy. The positive clinical dynamics of Axamon was confirmed by ENMG findings. In the patients in the main group, the speed of excitation propagation along the peripheral nerves increased significantly more than in the comparison group, indicating the activation of remyelination processes; the amplitude of M-response in the hand and foot muscles increased. For example, the impulse rate of the medianus nervus on the affected side was 45.3±1.3 m/s before the treatment and 61.2±1.2 m/s after the treatment ($p<0.05$), respectively, the impulse rate of the tibialis nervus on the affected side was 42.3±1.2 m/s before treatment and 48.7±1.0 m/s after treatment. It should be noted that in the comparison group, despite the regression of pain syndrome and increased ability to perform daily activities, no changes in pulse velocity (or other ENMG parameters) were registered.

The results of the study confirmed that Axamon is a powerful anticholinesterase drug of conductive action, the application point of which is primarily the efferent (motor) fibres of peripheral nerves.

An interesting result of the study was a decrease in the severity of pain syndrome on the visual analogue scale (VAS) (from 23,2±1,2 to 12,0±1,3 points; $p<0,05$), as well as a decrease in the severity of sensory disturbances in the affected areas. After the completion of therapy, an increase in the volume of active and passive movements on the affected side of the spine and a restoration of symmetrical distribution of muscle activity were noted. This observation confirms the presence of the antipain effect of Axamon, which broadens the scope of its use in patients with vertebrogenic dorsopathies. It is also noteworthy that the use of ipidacrine provides an opportunity to reduce the severity of crumpy pain, which, in particular, has been noted in the treatment of patients with diabetic polyneuropathy [5]. The clinical efficacy of ipidacrine in compression-ischaemic and traumatic peripheral neuropathies, as well as in facial neuropathy, has been shown to be significant. Application of the drug was accompanied by earlier onset of positive clinical effect, shorter periods of treatment, more complete restoration of motor functions, and effective elimination of pain syndrome. Thus, it was shown that timely treatment of patients with mononeuropathies resulted in the onset of the effect by 14-19 days, while the duration of recovery period was reduced by an average of 6.7±2.1 days [13]. Use of the drug was also associated with an increase in the number of patients with maximal recovery of impaired functions and a decrease in the severity of pain syndrome. As a rule, Ipidacrine was prescribed as part of a complex medication therapy (B-group vitamins, thioctic acid), therapeutic exercises and physiotherapeutic procedures.

Given the ability of ipidacrine to inhibit the activity of sodium channels and the resulting anti-pain

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activity, the possibility of using the drug to reduce the intensity of pain syndrome is of undoubted interest. Thus, the potential of ipidacrine in the treatment of patients with a combination of movement disorders and pain syndromes - lumbar pain caused by degenerative lesions of the spine - has been repeatedly studied.

The results of the use of ipidacrine in the treatment of patients with discogenic radiculopathy and myelopathy, as one would expect, were quite encouraging [10]. The severity of the patients' flaccid paresis against the background of the therapy decreased significantly, as did the intensity of pain syndrome due to the lesion of lumbar spinal roots, which had a neuropathic component. The positive effect on motor and sensory disorders was probably due to the known properties of the drug to enhance synaptic neuromuscular transmission, improve axonal conduction, and regulate the work of potential-dependent sodium pumps. Another study has shown that the use of ipidacrine is accompanied by a reduction in pain intensity not only in cases where there is a neuropathic component, but also in patients with dorsopathy not combined with radicular pain syndrome [11]. The study included patients with acute pain syndrome (duration over 3 weeks), some of whom did not have plexopathy and/or radiculopathy, which does not suggest that the analgesic effect of ipidacrine is related to blockade of sodium pumps, characterised by overactivity in chronic pain syndrome or neuropathic pain. It is possible that other mechanisms, not fully understood to date, may underlie the analgesic effect of ipidacrine in patients with dorsopathy. Further studies confirmed the effectiveness and feasibility of Axamon in the treatment of patients with dorsopathy at different stages of the disease course. In particular, its use was found to provide a more rapid onset of analgesic effect in patients with dorsopathy receiving a set of rehabilitation measures in outpatient settings [2]. The authors noted that the simultaneous use of Axamon and Pantogam had a pronounced anti-pain effect and was as effective as nonsteroidal anti-inflammatory drugs (NSAIDs). Pain intensity during therapy decreased from 15.1±1.1 to 11.0±1.3 points (p=0.02), and was more pronounced than patients not treated with Axamon. A decrease in pain intensity was observed both at rest and during physical activity, which provided an extension of the motor mode in the patients observed. A notable result was a significant reduction in the severity of anxiety and asthenic disorders, which was observed during treatment with Axamon or Axamon and Pantogam, but was absent in patients receiving only NSAIDs and non-medicinal treatment (comparison group). As in other studies investigating the efficacy and tolerability of Axamon, the authors noted the absence of clinically significant side effects, in particular negative effects on the cardiovascular, hepatobiliary and gastrointestinal (GI) systems. This observation is of great practical importance in view of the high risks of organ and systemic complications, which increase with NSAIDs, especially in patients with comorbid conditions and in the elderly.

A separate study was dedicated to the effectiveness of ipidacrine in patients with various forms of lumbar dorsopathy with radicular syndrome, particularly after discectomy without regression of pain intensity (failed spinal surgery syndrome). In accordance with the study protocol, ipidacrine was used as part of a combination therapy that included prescription of NSAIDs, topical administration of drugs and non-medicinal therapy. The results of the study showed that the combined therapy with ipidacrine contributed not only to a more complete recovery of motor function (the results of dynamic clinical observation were confirmed by electrophysiological examination), but also to a reduction in the severity of radicular pain syndrome. The authors of the study also noted good treatment tolerance, no negative effects of ipidacrine on the cardiovascular system and gastrointestinal organs, and the absence of a generalised cholinomimetic effect. A particular feature of the patients included in this study was radiculopathy, characterized by features of neuropathic pain syndrome (absence of nociceptor irritation, pervasive pain, often with an unpleasant hyperpathic tone, which is difficult to describe with common semantic descriptors). The anti-pain effect of ipidacrine in this situation is likely to be due to its effect on the sodium potential-dependent channels of the neuron axon.

An important area of application of Axamon is the treatment of patients with facial neuropathy. This disease is quite widespread in the population, and its consequences in the form of a significant cosmetic defect often limit the patient's ability to work and reduce their quality of life. Anticholinesterase drugs are widely used to treat patients with facial neuropathy. The use of this group of drugs has demonstrated some efficacy in these patients, but their use requires caution, as it is associated with the risk of contracture of the facial musculature. Importantly, studies investigating this problem have demonstrated the safety of ipidacrine, particularly the absence of an increase in the number of patients with contractures of the facial muscles. Numerous studies

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have shown that the use of ipidacrine in patients with facial neuropathy is accompanied by a significant clinical effect in the form of a reduction in the time to achieve maximum full recovery of motor functions of the facial musculature, increasing the number of patients who have achieved full recovery . Thus, in the work of T.T. Batysheva et al. it was found that the use of ipidacrine in the complex treatment of patients with facial neuropathy with duration of disease over 10 days (but less than 2 months) in 2 times accelerates the recovery of motor function of facial nerve, without leading, in contrast to treatment with neostigmine methylsulfate, to the development of facial muscle contracture. 78 patients with facial nerve neuropathy were examined and divided into 3 groups. Group 1 patients were treated with neostigmine methyl sulfate 1.0 ml subcutaneously for 10 days, then 5 mg for 20 days, pentoxifylline 100 mg 3 times daily, B-group vitamins. Group 2 patients received ipidacrine 20 mg 2 per day for a month against a background of the same treatment as Group 1, except for neostigmine methylsulfate. Group 3 patients, along with therapy in Group 2 have received thioctic acid intravenously by drip 600 mg once a day, then 600 mg orally for 20 days, alpha-tocopherol acetate 40 mg, vitamin C 100 mg 2 times a day for a month, nicotinamide intramuscularly 2 ml for 10 days. The recovery of motor activity according to clinical and neurological examination was observed in Group 1 after an average of 2.5 weeks, in Group 2 and 3 - after 1.8 and 1.2 weeks. Complete recovery by the end of the course of treatment was observed in 34% of the 1st group, 61% and 72% in the 2nd and 3rd groups respectively. The use of ipidacrine in patients with facial neuropathy increases the effectiveness of treatment by an average of 2.5 times, which allows reducing the duration of the recovery period by an average of 8.5±3.5. Aksamon application is possible from the first day of the disease, duration of treatment is determined by specific conditions - patient's condition, severity of motor deficit, effectiveness of treatment carried out. Axamon in patients with facial neuropathy is prescribed up to 60-80 mg/day in 3-4 intakes. Other drug and non-drug therapies must be used at the same time.

Axamon in 20 mg tablets and 5 mg/ml and 15 mg/ml solution for injection. Epidacrine is adsorbed in the duodenum, to a much lesser extent in the stomach and is 40-55% bound to blood proteins. Maximum concentration of ipidacrine in blood after oral administration is reached one hour after administration, half-life of the drug is 0.7 hours. The drug is eliminated from the body mainly by the kidneys, although there are extrarenal mechanisms of its elimination (secretion with bile and biotransformation). Epidacrine takes effect 5-10 minutes later than neostigmine methylsulfate and has a less pronounced but longer (3-5 hours) effect compared to neostigmine methylsulfate (2.0-2.5 hours).

CONCLUSION:

The current results of experimental and clinical studies demonstrate a wide potential of Axamon for the treatment of patients with various clinical manifestations of peripheral nervous system disorders. It has a significant effect on motor and sensory components of the nervous system in therapeutic doses. Axamon is comparable with many other anti-pain drugs in terms of its effectiveness, while the incidence of side effects of its use is negligible. It also has a good risk-benefit ratio in the treatment of patients with peripheral paresis, which distinguishes it from the classical peripheral AChE inhibitors. Proper choice of indications for prescribing Axamon, careful selection of the daily dosage and duration of treatment can maximise the effect of its use.

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