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Research Article

Parkon® in the treatment of multiple sclerosis. A pilot study

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Multiple Sclerosis (MS) is one of the most common chronic demyelinating diseases of the central nervous system. The disease affects and relatively quickly leads to disability in mainly people 15-40 years of age. The development of MS can occur progressively or with exacerbations and remissions. The pathogenesis of the disease is based on an autoimmune process directed against myelin or myelin-producing CNS oligodendrocytes. In recent years, in the mechanisms of death of myelin-synthesizing oligodendrocytes, more and more attention has been paid to metabolic shifts. An important role is played by the activation of astro- and microglia, impaired neurotransmitter metabolism and apoptosis. In the occurrence and enhancement of these neurometabolic changes, an important role is played by the enhancement of the endogenous processes of lipid peroxidation and the suppression of antioxidant systems [1].

In the treatment of exacerbations of MS, hormonal therapy with corticosteroids, which have immunosuppressive, anti-inflammatory, immunomodulatory and antioxidant properties, is preferred. However, it is known that side effects of drugs of this group significantly complicate their use. An important point in the treatment of MS is preventive therapy in order to prevent exacerbations and slow down the course of the disease. The disadvantages of these therapy include uncontrolled selectivity of action and the inability to reduce existing symptoms. A big problem for MS patients is also an improvement in the quality of life during remissions. In these cases, symptomatic therapy with antispastic agents, antidepressants and antioxidants is used.

To solve these and other unresolved issues in the treatment of PCs, it is necessary to search for new drugs and treatment methods. To this end, we tried to use the new Russian drug Parkon® (hereinafter - Parkon) in patients with various forms of MS. Parkon's first target area of application at the time of its creation was the treatment of Parkinson's disease and other extrapyramidal diseases. At the same time, experience with the use of this drug has demonstrated significantly greater opportunities for the use of Parkon in neurological patients. The main distinguishing feature of Parkon is associated with the reflex action of some exogenous Reactive Oxygen Species (ROS) on brain tissue metabolism by stimulating receptors in the nasal mucosa. The signal entering the brain causes reflex modulation of the activity of the structures of the hypothalamic-pituitary complex, the induction of antioxidant enzymes and a decrease in the formation of prooxidants. Taken together, these properties offer ample scope for Parkon's use in neurology.

In the mechanisms of Parkon's therapeutic action, a number of adaptogenic effects can be distinguished. Among them are functional activation of the adenohypophysis, an increase in the production of endogenous cortisol, a decrease in endogenous oxidative stress in the tissues of the central nervous system, and reflex regulation of neurotransmitter interactions [2,3]. The positive effect of Parkon and some other exogenous ROS on neurotransmitter mechanisms is realized by inhibiting the activity of Monoamine Oxidases (MAO) in the hypothalamus, basal ganglia and brainstem [2] and by reducing the activity of diamine oxidases in the brain [4]. This normalizes the activity of the neurotransmitter systems of mono- and diamines (serotonin, catecholamines, histamine) at the level of the hypothalamus, brainstem, cortical trunk, cerebellar cortex and other structures. Taken together, these effects may underlie the improvement in motor symptoms and Parkon's antidepressant effect. It is also known that

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other exogenous ROS activate aerobic metabolism and induce macrophage activation. This includes the previously established non-specific stimulation of the endogenous interferon system by ROS-activated macrophages [4], which may have a special place in the clinical effects of Parkon.

Thus, the therapeutic effect of Parkon develops due to a complex modulating effect on the basic physiological and biochemical processes in various brain structures. All these properties of Parkon can contribute to the slowing of the pathological process, reducing the severity and duration of exacerbations, as well as reduce the external manifestations of MS. This article presents the results of the first clinical study of the efficacy and clinical safety of Parkon in patients with MS.

Patients and methods

The study was conducted according to an open scheme. Thirty patients (13 men and 17 women) aged 26 to 56 years (mean age 42.0 ± 10.0 years) with various forms of the course of the disease were examined. Among them, 7 people - with a remitting forms, 3 - with a primary progressive, 5 - progressing with exacerbations, and 15 - with a secondary progressing form. 27 patients were in remission and 3 patients in the stage of subsiding exacerbation. In 29 patients, the cerebrospinal form of the disease was diagnosed, and in 1 patient - cerebral.

The duration of the disease averaged 11.4 ± 7.0 years (from 1 to 25). The severity of the condition on the Kurtske scale of disability degree averaged 4.5 points. By the beginning and during the study, all patients received common drug therapy. Vascular and metabolic therapy was received by 18 people, sedatives - 5, muscle relaxants - 5, copaxone - 2, supporting hormonal therapy - 2 patients.

Each subject underwent a clinical neurological examination, questionnaire and electrophysiological studies.

A quantitative assessment of motor impairment was carried out using the Kurtske functional systems damage scale and the Kurtske multiple sclerosis rating scale [5]. Questionnaire methods were used to assess depression (according to the Beck questionnaire), anxiety (according to the Spielberger questionnaire), and the quality of night sleep. From electrophysiological methods, we used the study of short-latency somatosensory evoked potentials, SSEP, and transcranial magnetic stimulation, TMS [6,7]. All data were evaluated before and after treatment. A clinical neurological study was conducted taking into account the scale for assessing the degree of reliability of the diagnosis of multiple sclerosis by Poser [8]. The control group in assessing electrophysiological parameters was 12 healthy subjects, 7 men and 5 women, whose average age (40.8 ± 6.7 years), did not significantly differ from the age in the population of patients with multiple sclerosis.

To assess SSEP, tibial nerve stimulation was used on the inner part of the ankle with rectangular pulses of 0.1 ms duration, 5 Hz, and an intensity 3-4 times higher than the sensory threshold. The recording electrodes were located at the points Cz – Fpz according to the international 10–20 system. The sensitivity of the amplifier was set in the range of 1–2 μV / div. with a frequency band of 10 Hz to 3 kHz. The analysis period was 100 ms, the number of averages = 2000. TMS was performed with single stimuli; analyzed the time of central motor conduction (VCMP), the time of the threshold of the appearance of the evoked motor response (WMO) and the duration of the WMO with m. Abduktor pollicis brevis and m. Biceps brachii. Parkon was prescribed for 2 introductions in each nasal passage with a break of 10-15 s, 3 times a day for one month. Statistical processing of the data obtained in the study of SSEP was carried out according to the nonparametric Whitney-Mann criterion, the remaining data were processed according to the t-student criterion.

At the initial examination, in 28 patients (93%), pyramidal symptoms and coordination disorders of varying severity were noted. Disorders in the cranial innervation and pelvic function were detected in 21 patients (70%), a decrease in deep and / or superficial sensitivity was detected in 20 patients (67%). Depression on the Beck scale was observed in 77% of patients; an increased level of anxiety on the Spielberger scale was detected in all patients. Sleep disorders were detected in 45% of patients.

Twenty-five people underwent re-examination after Parkon's therapy, 3 of them with a remitting, 3 with a primary progressing, 5 progressing with exacerbations, and 14 with a secondary progressing course. Only 5 people dropped out of the study, of whom two patients with a relapsing remission dropped out due to an exacerbation of the disease, one patient refused a second visit, and in two patients the drug was canceled due to side effects. Side effects in the form of dry mucous membranes of the nose and dry cough appeared a few days after the start of the drug and regressed independently after its cancellation. No other side effects have been identified.

The impact of Parkon on neurological and affective disorders

As a result of treatment, we observed varying degrees of improvement in patients. Imbalances in coordination (according to the Kurtzke scale) decreased by 15% from the initial level in 40% of the examined patients. This improvement was mainly due to a decrease in the severity of deliberate and postural tremor. Depression and anxiety rates on the Beck and Spielberger scales decreased, respectively, by 10% and 17% in 70% of patients. Sleep quality improved by 14% from baseline in 90% of patients (Table 1).

To evaluate Parkon's effect in various MS, the analysis of the results was carried out for each of the following groups of patients: with remitting course, with primary progressing, progressing with exacerbations and with secondary progressing course. The analysis showed that the most pronounced improvement in the indicators occurred mainly in patients with a secondary progressive course (Table 2).

A more pronounced improvement in a number of indicators (coordination, sleep quality and depression) in this subgroup may indicate a higher sensitivity to Parkon therapy in patients with a secondary progressive course of multiple sclerosis. In

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Table 1: The effect of Parkon on neurological and affective disorders in patients with MS: The general population of patients.

Scales and Questionnaires	Mean (M ± SD)		Improvement
	Before treatment	After treatment	
Functional System Damage Scale (J. Kurtzke):			
Pyramidal syndrome	2.8±1.6	2.6±1.5	10%; n.s.
Impaired coordination	2.4±1.1	2.0±0.9*)	15%
Cranial nerve disorders (except for the II pair)	1.3±0.9	1.2±0.9	7%; n.s.
Sensory Disorders	0.8±1.0	0.7±1.0	11%; n.s.
Pelvic disorders	1.1±0.9	1.1±1.0	not
Optic nerve lesions	1.0±1.1	1.0±1.1	not
Intelligence changes	0.6±0.7	0.6±0.7	not
Disability Rating Scale	4.6±1.7	4.2±1.8*)	8%
Questionnaire rating:			
Sleep quality	19.8±1.9	22.6±3.2*)	14%
Anxiety level (according to Spielberger)			
actual	55.2±7.7	50.0±6.9*)	9,5%
usually	57.6±4.8	51.9±6.0*)	10%
Depression (Beck scale)	19.7±10.9	16.3±10.2*)	17%
Significant changes are indicated everywhere: *) $p \le 0.05$; n.s. = not significant			

Table 2: The effect of Parkon on neurological and affective disorders: a subgroup of patients with secondary progressive course of MS.

Scales and Questionnaires	Mean (M ± SD)		Improvement
	Before treatment	After treatment	
Functional System Damage Scale (J. Kurtzke):			
Pyramidal syndrome	3.0±1.7	2.8±1.6	6%; ns
Impaired coordination	2.7±1.0	2.0±0.6*)	25%
Cranial nerve disorders (except for the II pair)	1.5±1.0	1.3±1.0	11%; ns
Sensory Disorders	1.0±1.3	1.0±1.3	no
Pelvic disorders	1.2±1.2	1.2±1.2	no
Optic nerve lesions	0.8±0.4	0.8±0.4	no
Intelligence changes	0.7±0.5	0.7±0.5	no
Disability Rating Scale	5.0±1.5	4.6±1.8*)	8%
Questionnaire rating:			
Sleep quality	19.7±1.8	23.1±4.1*)	17%
Anxiety level (according to Spielberger)			
- actual	57.2±5.9	51.0±4.5*)	11%
- usually	60.0±4.1	52.8±5.7*)	12%
Depression (Beck scale)	18.4±6.8	13.4±9.1*)	27%

this group, the results of treatment with Parkon were also compared for other indicators - TMS and SSEP.

The impact of Parkon on the performance of TMS

When examining patients with TMS before treatment, in 5 patients (17%) the *evoked motor response* from m. Abduktor pollicis brevis and from m. Biceps brachii was not obtained. In other patients time of central motor conduction, the duration and threshold of the appearance of WMO compared with those in healthy subjects were increased. These results are generally consistent with the literature, where in patients with MS there are violations of almost all parameters that are usually analyzed during TMS with single stimuli: VCMP, the threshold for the appearance of WMO and its various characteristics [7].

After Parkon's treatment, no significant changes in TMS were found in the group as a whole (Table 3).

At the same time, there was a slight improvement in the average WMO indicators: by m. Abduktor pollicis brevis VCMP decreased by 7%, the duration of WMO by 3%, the appearance threshold by 18%; with m. Biceps brachii VCMP and the duration of WMO decreased by 7%, the threshold by 18%. In 5 patients (20%), as before treatment, WMO with m. Abduktor pollicis brevis and with m. Biceps brachii has not been obtained. The latter is consistent with data from Caramia, et al. [7], that in these patients WMO is not recorded in 20-30% of the examined muscles.

A study of TMS during Parkon's therapy in a subgroup of patients with a secondary progressive course of MS also did not show a significant improvement (Table 4).

We note that with the same positive dynamics of changes, the average values of TMS indicators (except for the threshold) before treatment in this subgroup were slightly higher than in the general group (compared to Table 3). It is to note also the same direction and magnitude of positive changes of the threshold in the general group of patients and in the subgroup of patients with a secondary progressive course of the disease.

Parkon effects on SSEP

As a result of the SSEP study in patients, a significant ($p < 0.005$) increase in the latent periods of the P38 components and a decrease in the P38 / N46 amplitude were found in comparison with healthy subjects. A similar lengthening of

Table 3: The effect of Parkon on TMS in patients with multiple sclerosis: the patient population as a whole (a group of healthy subjects of 12 people was taken as the norm).

Indicators	Before treatment	After treatment
m. Abduktor pollicis brevis:		
VCMP (norm 7.7 ms)	17.8±6.7	16.5±6.1
duration of the WMO (norm 16.8 ms)	18.2±7.4	17.6±7.0
threshold of the WMO appearance (norm 40%)	55 %	45 %
m. Biceps brachii:		
VCMP (norm 5.1 ms)	9.8±3.5	9.1±3.2
duration of the WMO (norm 23.3 ms)	29.2±4.2	27.2±3.5
threshold of the WMO appearance (norm 40%)	55 %	45 %

Table 4: The effect of Parkon on TMS in patients with multiple sclerosis: a subgroup of patients with a secondary progressive course of MS.

Indicators	Before treatment	After treatment
m. Abduktor pollicis brevis:		
VCMP (norm 7.7 ms)	18.1±6.0	17.5±5.3
duration of the WMO (norm 16.8 ms)	18.5±6.9	18.1±6.7
threshold of the WMO appearance (norm 40%)	55 %	45 %
m. Biceps brachii:		
VCMP (norm 5.1 ms)	11.6±3.1	10.9±2.9
duration of the WMO (norm 23.3 ms)	31.4±4.5	29.2±3.3
threshold of the WMO appearance (norm 40%)	55 %	45 %

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latencies and a decrease in amplitude in patients with multiple sclerosis in excess of 60% was found in Sand, et al. [9]. In the study of patients' SSEP after therapy with Parkon, a certain shortening of the latent periods of the components P38 and N46 was noted, as well as a significant, 50% increase in the amplitude of P38 / N46 (Table 5). Nevertheless, this indicator remained below normal values and is consistent with Andersen data [4] obtained in the study of evoked potentials in patients with a verified diagnosis of MS.

A study of SSEP during Parkon's therapy of patients with a secondary progressive course of MS also did not reveal a significant improvement in the latency period of P38 and N46. However, we found an even more pronounced increase in the amplitude of P38 / N46, which after Parkon treatment increased by 75% in this subgroup (Table 6).

Table 5: The effect of Parkon on SSEP in patients with MS: The patient population as a whole.

Indicators	Norm	Before treatment	After treatment
Latent period Components P38 (ms)	38.1±3.1	45.3±5.0	43.1±5.2
Latent Period Components N46 (ms)	46.2±2.9	54.6±6.1	52.1±5.8
Amplitude P38 / N46 (μV)	2.5±1.2	0.6±0.5	0.9±0.3

Table 6: The effect of Parkon on SSEP indicators in patients with MS: A subgroup of patients with secondary progressive course of MS.

Indicators	Norm	Before treatment	After treatment
Latent period Components P38 (ms)	38.1±3.1	45.9±5.8	44.2±6.1
Latent period Components N46 (ms)	46.2±2.9	56.6±6.0	54.3±6.9
Amplitude P38 / N46 (μV)	2.5±1.2	0.4±0.3	0.7±0.3

Conclusion

Our data indicate a positive effect of Parkon's therapy in patients with MS. The most significant effects were achieved in the field of affective disorders. After a month of using Parkon, a significant decrease in anxiety and depression was found, as well as an improvement in sleep quality in most patients examined. Positive dynamics was noted in the automotive sector. We noted a significant decrease in coordination abnormalities in 40% of patients, mainly due to a decrease in intentional and postural tremor.

The reaction of pyramidal disorders to therapy with this drug is less pronounced. This is evidenced by the absence of a significant improvement in neurological symptoms and magnetic stimulation data. The clinical symptoms of sensory disturbances and somatosensory evoked potentials data also did not undergo significant changes, although there was a tendency to an improvement in SSEP.

We noted earlier that Parkon allows you to act on various neurohumoral and neurotransmitter mechanisms involved in the pathological process. However, steady stimulation of the hormonal system during Parkon therapy is formed only by the end of the 3rd–4th week of treatment. This is generally characteristic of the reaction of the hormonal system and suggests the possible further improvement of symptoms in patients with MS with a longer course of treatment. An additional argument in favor of this is the data of other clinical studies, indicating a steady improvement in motor functions, a decrease in tremor, as well as symptoms of asthenia in most patients after two to three months of treatment with Parkon.

The results presented in our article will undoubtedly stimulate further research in this area. At the same time, on the basis of the data obtained today, we can conclude that it is advisable to use Parkon as an additional therapeutic agent in patients with MS, especially with a secondary progressive form of its course.

Final remarks

The main characters of this article are MS and Parkon. MS is understandable, it is one of three "leaders" among organic diseases of the central nervous system (the other two are represented by epilepsy and parkinsonism). But why is Parkon a drug that contains very dilute hydrogen peroxide and has arisen from studies of other "active oxygen" $O_2^{\bullet -}$? ? In both cases, these are two "bad" molecules [10], the levels of which are regulated by antioxidants.

For the answer, we recall that earlier, using $O_2^{\bullet -}$, we learned not only how to successfully treat bronchial asthma [11], but also how to treat patients with Parkinson's disease [12] (by the way, this is where the patented name "Parkon"). Equally important is the fact that MS and Parkon have an important common purpose in the body. This is the blood-brain barrier (BBB). In Parkinson's disease, the BBB restricts the passage of endogenous peripheral substances such as dopamine from the blood to the brain, and in these cases Parkon and $O_2^{\bullet -}$ allow us to control (and regulate) the permeability of the BBB [13]. In contrast, in the case of multiple sclerosis, an abnormal increase in BBB permeability is a "first, early and persistent" event for the disease (personal communication from Professor A. Wein). The discovered method for the possible control of BBB permeability can open, in our opinion, good prospects for the regulation of the BBB permeability and the treatment of these diseases. The first steps in this direction have already been taken.

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