Peertechz


Clinical Group

Open Journal of Parkinson's Disease and Treatment

DOI:http://dx.doi.org/10.17352/ojpdt



**Golubev VL, Sadekov PA, Pilipovich AA, Goldstein NI***

Department of Human and Animal Physiology, Biological Faculty, Lomonosov Moscow State University, Moscow, Russia

**Received:** 04 March, 2019
**Accepted:** 18 March, 2019
**Published:** 19 March, 2019

***Corresponding author:** Goldstein NI, Ph.D. Department of Human and Animal Physiology, Biological Faculty, Lomonosov Moscow State University, Moscow, Russia, E-mail: goldexperte@googlemail.com; dr.naum.goldstein@gmail.com

https://www.peertechz.com



Research Article

# Parkon as a treatment of the Parkinson's disease

## Introduction

The application of the advancements in biophysics and biochemistry in medical science received a new impulse in the recent years. One of them was the discovery of superoxide radicals [1], in the inhaled atmospheric air and the vital role of this radical [2]. New views regarding the vital role of exogenous Reactive Oxygen Species (ROS) were developed [3]. ROS that enter the organism through the inhalation and regulate a series of vital functions receive most of the attention. The perception of the signal and the realization of the physiological effects of ROS are materialized by the receptor structure of the nasal cavity mucosa. New data on the role of these receptors, especially of the vomeronasal organ (VNO) [4], contributed to an understanding of the possible participation of this structure in the mechanisms of action exogenous ROS. It was determined that the signal travels from nasal cavity receptors to hypothalamus and causes the cascade of reflex responses in various structures of the brain. The excitement of the VNO structures activates serotonine (5-HT) neurons of the hypothalamus, 5-HT and norepinephrine neurons of the blue spot, stimulates the release of the dopamine (DA) in mesolimbic area of the brain [5].

It was revealed that inhalations of gas-phaseous superoxide and nasal applications of strongly diluted hydrogen peroxide solutions promote suppression of MAO-A and MAO-B activity and reduction of endogenous oxidative stress in the hypothalamus, brainstem and basal ganglia of healthy and MPTP-treated animals [6]. This causes the decrease in the production of endogenous oxidants that are a result of MAO-dependent catabolism of DA and 5-HT and decreases the intensity of the oxidation stress. The induction of the antioxidant system of the glutathione and catalase also contributes to the decrease in the oxidation stress. Some effects of the ROS are connected to reflex suppression of the lactotropic function [2], which leads to additional activation of DA-system.

Surprisingly was observed also that the inhaled superoxide leads to reduction of tremor and improves autonomic symptoms in cases of tremor associated with antipsychotic drug Orap™ containing Pimozide (Internal Goldstein & Lewin GmbH document 1998). These properties, combined, open the wide range possibilities for the application of exogenous ROS in neurology [7]. In particular, pathologic activation of MAO-B and oxidation stress in the basal ganglia structures are viewed to be important pathogenetic links in the development and progression of the Parkinson's disease. In terms of these perceptions the increase in MAO-dependent catabolism of DA impairs the metabolism of this mediator and promotes the increase of the endogenous oxidation stress and the destruction of the cell structures of the nigrostrial system. In this work we presented the results of the clinical use of ROS-containing drug of the new generation - Parkon for the treatment of the Parkinson's disease.

## Materials and Methods

Parkon [8], a composition of stabilized micromolar concentration of the pharmaceutical hydrogen peroxide, was used on 30 patients (19 male and 11 female). Among them 10 people had rigid-tremor form, 6 had tremor-rigid form and 14 had a mixed form of the Parkinson's disease. Mean age was 63±1.9 years (from 44 to 76 years), mean stage of the disease on Hoehn & Yahr 1.97±0.1 (from 1.5 to 3). Mean disease duration was 4.7±0.89 years (from 1 to 19 years). Rate of disease progression according to criteria by N. V. Fedorova: fast - 8 people, moderate - 17 people, slow - 5 people. 18 patients received Parkon in addition to other therapy with 1-dopa containing medication (Madopar); 12 people received Parkon as a monotherapy.

In order to conduct a detailed analysis of the effects of



**Citation:** Golubev VL, Sadekov PA, Pilipovich AA, Goldstein NI (2019) Parkon as a treatment of the Parkinson's disease. Open J Parkinsons Dis Treatm 2(1): 001-005. DOI: http://doi.org/10.17352/ojpdt.000006

Parkon's treatment there were the following paired groups for comparison.

1. Those who never received l-dopa containing medication (Parkon monotherapy) and those receiving Madopar (combination therapy Madopar + Parkon); there were no statistically significant differences between these subgroups in terms of age, stages of the disease, duration and quality of life.

2. Those who had the early and later stages of the disease; these groups also did not differ in age, duration, dosage of Madopar; only the quality of life among the patients with the 3rd stage of the disease was significantly lower before beginning of the treatment with Parkon (it was 77%).

3. Different variants of the Parkinson's disease (tremor-rigid, rigid-tremor and mixed). These subgroups did not differ in the quantity of observations, disease duration and mean daily dose of Madopar; however, patients with the mixed form of the Parkinson's disease were slightly younger compared to other subgroups and their disease did not progress to the 2nd stage and was around 1.8, while the tremor and rigid forms were on the second (2.0) and later (2.4) stages of the disease accordingly before the beginning of the treatment.

Parkon was prescribed according the following schedule: 2 times into each nostril with the 10-second delay, three times a day. At the same time the existing antiparkinsonian therapy remained in effect without any modifications until the end of the treatment. Each patient undergone the neurological, neuropsychological, electrophysiological and questionnaire investigation. Clinical neurological investigation was conducted using the criteria of the Parkinson's disease by Hughes [9]. Quantitative analysis of the motor function was performed using the Unified Parkinson's Disease Scale (UPDRS), the evaluation of the stages of the disease was performed according to the Hoehn & Yahr scale [10], and the evaluation of the daily activities - using the Schwab and England scale. The rate of the disease progression was evaluated according to N. V. Fedorova criteria [11].

The neuropsychological investigation included the quantitative evaluation of the general cognitive defect using the Mini Mental State Evaluation (MMSE) scale, qualitative and quantitative evaluation-Matisse dementia scale (evaluation of the attention, initiation, perseverance, conceptualization, and memory), evaluation of frontal lobes functions (conceptualization, speech speed), Schulte samples and the samples on verbal associations, and verbal memory was investigated by memorizing 10 words in the text.

Affective disorders were evaluated by means of the Hamilton scale and Beck scale. The evaluation of the vegetative disorders and the sleep quality was conducted using vegetative questionnaire and the quality of sleep questionnaire. All patients were subject to ElectroEncephaloGraphy (EEG - in 8-lead compress spectral analysis) with the evaluation of the absolute power (μWatt).

The evaluation of the motor, cognitive and affective disorders and electrophysiological parameters was performed before and after the treatment (in one month).

The efficacy of the treatment was evaluated using the efficacy coefficient in relation to the UPDRS. This method allows distinguishing four levels of the treatment's efficacy. In case of 1%-19% improvements the efficacy was considered "minimal" (score of 1); 20%-39% - "moderate" (score of 2); 40%-59% - "good" (score of 3); more than 60% -"excellent" (score of 4).

The statistical processing of the data was performed using the Student t-distribution (statistical program "SPSS 10").

## Study Results and Discussion

Overall, in the group, the major motor symptoms were hypokinesia, rest tremor, extrapyramidal rigidity and postural disturbances. The hypokinesia was present in all patients and was manifested in deceleration of the movements in the extremities, changes in the handwriting, gait disturbances, problems in the movement initiation, arising from the chair, turning in the bed, hypomimia and hypokinetic disarthria. The rest tremor was observed in 83% of the patients; rigidity - 93%; significant postural instability - 17% of the patients.

During the neuropsychological investigation all patients demonstrated various degrees of cognitive disturbances, however, none of them reached the level of dementia (mean MMSE score = 27).

### Effect of parkon on the whole group

During the course of the treatment with Parkon the patients' conditions improved: there was a statistically significant UPDRS scale improvement in daily living activities and motor section (Table 1). The treatment's efficacy after one month was 1.33 (23%), which corresponded, according to our criteria, to a slightly expressed medical effect.

There was a statistically significant improvement in the quality of life section of UPDRS: improvement in the handwriting - 8 people, reduced tremor - 8 people, reduction in sensory complaints -7 people; the quality of life score improved by 16.7% in 13 people. In the motor disturbances examination there was a statistically significant reduction in axial rigidity of the extremities by 35% in 17 people, reduction in the action tremor - 32% in 9 patients, improvements in bradykinesia: finger taps - 26% in 12 patients, making a fist 35% - 17 patients, reduction in the action tremor - 46% in 10 people, diadochokinesia - 39% in 16 patients. There was a tendency to reduce the rest tremor and bradykinesia in the legs. The combined score in the motor examination significantly decreased after the treatment with Parkon by 24% in 18 people. The total score decreased in 18 patients by 23%, which corresponded, according to our criteria, to the moderate effect. There was no statistically significant deterioration in any item of the UPDRS scale.

In the affective sphere, there was a statistically significant reduction in the level of depression on the Hamilton scale by 19% in 12 people (from 7.11±1.2 to 5.78±1.0). The values of the neuropsychological parameters after the treatment remained the same.



**Citation:** Golubev VL, Sadekov PA, Pilipovich AA, Goldstein NI (2019) Parkon as a treatment of the Parkinson's disease. Open J Parkinsons Dis Treatm 2(1): 001-005. DOI: http://doi.org/10.17352/ojpdt.000006

Table 1: Mean UPDRS values before and after the treatment with Parkon.

| UPDRS | Baseline | After treatment | Improvement % | P |
|---|---|---|---|---|
| Handwriting | 1.06 | 1.78 | 26% (8 people) | T |
| Tremor | 1.28 | 1.06 | 17(8 people) | <0.1 |
| Sensitivity | 1.56 | 1.33 | 41 (7 people) | T |
| Quality of Life (total) | 7.06 | 5.89 | 16 (13 people) | <0.05 |
| Rest Tremor | 3.11 | 2.56 | 17(11 people) | T |
| Action Tremor (right hand) | 3.78 | 2.50 | 36 (8 people) | T |
| Total Tremor Score | 1.22 | 2.83 | 32 (9 people) | |
| Neck Rigidity | 1.78 | 1.11 | 37 (13 people) | <0.05 |
| Right Hand | 1.94 | 1.78 | 17 | T |
| Left Hand | 1.83 | 1.56 | 32 | T |
| UPDRS | Baseline | After treatment | Improvement % | P |
| Handwriting | 1.06 | 1.78 | 26% (8 people) | T |
| Tremor | 1.28 | 1.06 | 17(8 people) | <0.1 |
| Sensitivity | 1.56 | 1.33 | 41 (7 people) | T |
| Quality of Life (total) | 7.06 | 5.89 | 16 (13 people) | <0.05 |
| Rest Tremor | 3.11 | 2.56 | 17(11 people) | T |
| Action Tremor (right hand) | 3.78 | 2.50 | 36 (8 people) | T |
| Total Tremor Score | 1.22 | 2.83 | 32 (9 people) | |
| Neck Rigidity | 1.78 | 1.11 | 37 (13 people) | <0.05 |
| Right Hand | 1.94 | 1.78 | 17 | T |
| Left Hand | 1.83 | 1.56 | 32 | T |
| Right Leg | 1.67 | 1.33 | 50 | <0.1 |
| Left Leg | 1.72 | 1.44 | 39 | T |
| Total Rigidity Score | 4.94 | 3.22 | 35 | <0.05 |
| Tapping (right hand) | 1.33 | 3.89 | 33 | <0.1 |
| Left Hand | 1.39 | 1.17 | 16 | <0.1 |
| Total Score | 2.72 | 2.00 | 26 | <0.05 |
| Fist (right hand) | 2.67 | 2.28 | 58 | <0.1 |
| Total Score | 1.44 | 2.78 | 46 | <0.1 |
| Diadochokinesia (right hand) | 1.00 | 2.50 | 50 | <0.05 |
| Left Hand | 1.17 | 2.83 | 29 | <0.05 |
| Total Score | 2.17 | 1.33 | 38 | O.05 |
| Leg Agility (right) | 2.61 | 1.33 | 46 | <0.1 |
| Left | 1.44 | 1.00 | 30 | T |
| Bradykinesia | 1.44 | 1.28 | 11 | T |
| Motor Disturbances Score | 22.67 | 17.17 | 24 | 0.05 |
| Total Score | 32.28 | 24.83 | 23 | <0.05 |

No effect on the vegetative parameters and the quality of the night sleep (according the questionnaire) was reported.

Parkon's effect on electrophysiological parameters was manifested in statistically significant reduction in the power of the bioelectrical activity predominately in the range of p2-rhythm in the frontal-temporal and sinciput-occipital leads on the left and the right. In addition, there was a decrease in the power of the pi activity in the right temporal and the occipital leads.

Therefore, it was determined that Parkon significantly improves the quality of life for patients with the PD, has a positive impact on the motor symptoms of the disease, especially rigidity, and decreases the level of depression. Also, Parkon has a positive impact on the EEG activity of the brain in terms of diffuse decrease in the rhythm's power.

## Parkon's effect on the patients in mono- and combination therapy (levodopa)

Comparing the group of patients receiving Madopar (1st group) to those who did not receive any dopa-containing medication ("Zero" group") there were significant differences in neurological parameters of the UPDRS scale.

In the 1st group there were significantly more severe disturbances during dressing, more expressed rest tremor, and presence of the "off" periods. There were no significant differences in EEG between the groups before the treatment.

After the course of the treatment with Parkon the differences between the groups increased due to the changes in the 1st group (patients receiving Madopar), where we observed significant improvements in the neurological symptoms. In this group 9 patients developed significant improvement in the quality of life part of the UPDRS score, 13 patients demonstrated a 26% decrease in the motor disturbances part of the UPDRS scale, 14 patients demonstrated the decrease in rigidity by 41%, bradykinesia (diadochokinesia -by 38% in 11 patients, finger tap - by 27% in 8 patients, leg agility - by 33% in 6 people); total UPDRS score improved by 25% in 13 patients. In addition, there was a tendency to an improvement in handwriting, decrease in the rest and action tremor, improvements in making a fist and general decrease in the bradykinesia. In zero group, a tendency to a decrease in bradykinesia was noted in finger tap and diadochokinesia tests. The treatment was more effective in the 1st group, the effect was "moderate", the score = 1.54 (25%). In Zero group, the effect was "minimal" - score = 1 (15%). Both groups demonstrated a trend of a decrease in the level of depression according to the Hamilton scale.

In EEG, the most noticeable changes occurred in the 1st group of patients. There was a statistically significant decrease in the power of the p2-rhythm in the frontal, parietal and central left leads.

Therefore, Parkon was more effective in patients receiving dopa-containing medication (Madopar) compared to the patients receiving Parkon as a monotherapy. In the group of patients receiving Madopar, as well as in the group in general, the most visible response was observed in patients with rigidity and bradykinesia.

## Parkon's effect on patients with different stages of a disease

After the treatment with Parkon, statistically significant positive changes were observed in the group of patients with the 2nd stage of the PD. In this group there was a significant improvement (19%) of the total quality of life UPDRS score in 7 patients, handwriting improvement and decrease in the action



Citation: Golubev VL, Sadekov PA, Pilipovich AA, Goldstein NI (2019) Parkon as a treatment of the Parkinson's disease. Open J Parkinsons Dis Treatm 2(1): 001-005. DOI: http://doi.org/10.17352/ojpdt.000006

tremor by 40% in 10 patients, bradykinesia (finger tapping) by 36% in 8 patients, diadochokinesia - by 29% in 9 patients; making a fist, leg agility and significant decrease of the total motor disturbances UPDRS score by 22% in 11 patients and total UPDRS score by 23% in 11 patients. The Parkon[5] s efficacy in this group was "moderate" and it was significantly better than in group 1 (stage 1). In 9 patients, there was a significant improvement (20%) on the Hamilton depression scale. There were no statistically significant improvements in groups 1 and 3.

Therefore, Parkon was most effective for patients with the 2nd stage of the disease (patients with two-sided effects but without postural disturbances).

### How does parkon influence the patients with various forms of the PD?

While comparing patients with different forms of the PD, it was observed that the greatest number of parameters that improved during the treatment were in the group of patients with mixed form of the disease. In this group, 7 people demonstrated 16% improvement in the quality of life, 8 patients - 35% decrease in rigidity; bradykinesia in tests on finger tap - decreased by 24% in 6 people, making a fist - by 53% in 6 people, diadochokinesia - by 37% in 7 people, total motor examination score decrease by 17% in 8 patients and the total UPDRS score improved by 18% in 8 patients.

In the 2nd group, predominately rigid form, the motor disturbances score improved by 39% in 5 people and total UPDRS score by 35% in 5 people. Also, there was a significant decrease in bradykinesia (tests on diadochokinesia) by 54% in 5 patients. There was a trend to decrease the rigidity and the action tremor.

Patients with a predominance of tremor over rigidity were least likely to respond to the therapy, however, even in this group there was a 16% improvement in the motor disturbances score of the UPDRS scale in 4 people, and, also, there was a trend of a decrease of rigidity and the total UPDRS score. The efficacy of the treatment in the 1st, 2nd and 0 groups were 19% ("minimal"), 35% ("moderate") and 18%) ("minimal") accordingly.

Therefore, Parkon was most effective in the PD patients with predominance of rigidity and hypokinesia and was less effective in tremor forms.

## Conclusion

Parkon *per se* is not an inhibitor of substrate forms of MAO. The physiological and therapeutic effect of the drug manifest of the reflex effects of exogenous ROS on the metabolism of the endogenous MAO inhibitors (for example Tribulin or Isatin) or regulatory functions of various brain structures, as was shown in the references [2,12-15]. In PD the investigation of Parkon's efficacy demonstrated that this agent can significantly improve quality of life and expressivities of the motor disturbances in 60% of PD patients (overall, out of 30 patients in the study 18 patients responded to the treatment). The degree of Parkon's efficacy depends on the form of the disease, its stage and the accompanied therapy. The greatest efficacy was demonstrated in patients with rigid-tremor form and a moderate degree of the disease (stage 2 with two-sided symptoms without the postural disorders), and when used in addition to Madopar (maximum effect). At the same time, patients with early stages of the disease, as well as the later stages, are less likely to respond to Parkon's treatment.

The agent affects rigidity and hypokinesia better than tremor. Also, positive effect of Parkon on depression was established. Considering the discovered therapeutic properties of Parkon, its efficacy can be increase considerably by the purposeful selection of the patients for the treatment. In this study Parkon had no impact on the postural and gait disturbances, presence and the duration of dyskinesia and the „off" periods. We were unable to determine Parkon's impact on cognitive ability, vegetative parameters and sleep quality of the PD patients. In this series of the investigation there were no occurrences of side effects. Another multicenter double-blind placebo-controlled study of Parkon on Parkinson's disease and medicinal induced parkinsonism showed a good therapeutic effect in Parkinson's disease and drug induced parkinsonism at the disease stage (Hoehn and Yahr) 1.0-2.5 in patients with predominantly trembling and rigid forms of the disease [16].

## References


1. Goldstein NI, Goldstein RN, Merzlyak MN (1992) Negative air ions as a source of superoxide. Int J Biometeorol 36: 118-122. Link: https://goo.gl/u9KXm4
2. Goldstein N, Arshavskaya T (1997) Is atmospheric superoxide vitally necessary? Accelerated death of the animals in a quasi-neutral electric atmosphere. Biosciences 52: 396-404. Link: https://goo.gl/bF8yPZ
3. Goldstein NI (2002) Reactive Oxygen Species as Essential Components of Ambient Air. Biochemistry 67: 194-204. Link: https://goo.gl/WvDB4L
4. Wysocki CK, Meredith M (1987) The vomeronasal system. Neurobiology of taste and smell // Editor T.E. Finger. - Wiley. NY 125-150.
5. Mitchell JB, Gratton A (1992) Mesolimbic dopamine release elicited by activation off the accessory olfactory system: a high speed chronoamperometric study. Neurosci Lett 140: 81-84. Link: https://goo.gl/5yfFcE
6. Goldstein N I (2000) Biophysical aspects of the physiological effect of exogenous $O_2^{\bullet -}$ on animals. PhD Thesis. Biofizicheskiye aspekty fiziologicheskogo deystviya ekzogennogo $O_2^{\bullet -}$ na zhivotnykh, Moscow, MGU, 2000 (*In Russian*).
7. Goldstein NI (2003) Use of gaseous superoxide $O_2^{\bullet -}$ in the clinic // Primeneniye gazoobraznogo superoksida $O_2^{\bullet -}$ v klinike, Russian Medical Magazine 4: 49-53.
8. Parkon (2005) Register of medicines of Russia RLS 12: 687. Link: https://goo.gl/Zwqa5L
9. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55: 181-184. Link: https://goo.gl/By1sXy
10. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17: 427-442. Link: https://goo.gl/GZwdz1
11. Кулуа ТК, Федорова НВ (1996) Factors affecting the quality of life of patients with Parkinson's disease. In: Parkinson's disease and movement disorders. In: Bolezn' Parkinsona i rasstroystva dvizheniy. M. 2017: 199-201.




**Citation:** Golubev VL, Sadekov PA, Pilipovich AA, Goldstein NI (2019) Parkon as a treatment of the Parkinson's disease. Open J Parkinsons Dis Treatm 2(1): 001-005. DOI: http://doi.org/10.17352/ojpdt.000006

12. Goldstein N, Rehberg G, Voskresenskaya O (1996) Die Inhalation von Superoxid potenziert die analgetische Wirkung niedrig dosierter Analgetika bei Menschen. Der Schmerz, 1997; Band 11, Heft 1, S. 67.

13. Goldstein N, Lewin Th, Kamensky A (1996) Exogenous gaseous superoxide potentiates the antinociceptive effect of opioid analgesic agents, Inflamm Res 45: 473-478. Link: https://goo.gl/kE34Cg

14. Gol'dshtein NI, Voskresenskaya OG, Dubynin VA, Levitskaya NG, Kamenskii AA (2003) The potentiating effect of gaseous superoxide on the effects of low doses of non-narcotic analgesics. Byulleten' eksperimental'noy biologii i meditsiny 135: 218-220. Link: https://goo.gl/r5V1BN

15. Goldstein N, Goldstein R, Terterov D (2012) Blood–Brain Barrier Unlocked. Biochemistry (Moscow) 77: 419-424. Link: https://goo.gl/PkLdef

16. Goldstein NI, Naidin VL, Fedorova NV (2002) The use of endonasal applications of the medicine Parkon in the complex treatment of Parkinson's disease. Primeneniye endonazal'nykh applikatsiy preparata Parkon v kompleksnom lechenii bolezni Parkinsona. Journal of Neurology 7: 45-48.







**Citation:** Golubev VL, Sadekov PA, Pilipovich AA, Goldstein NI (2019) Parkon as a treatment of the Parkinson's disease. Open J Parkinsons Dis Treatm 2(1): 001-005. DOI: http://doi.org/10.17352/ojpdt.000006