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Research Article

# Antidyskinetic activity of new derivatives of inydazol-4,5-dicarbonic acid in a parkinsonism experimental model due to administration of 6-hydroxydopapine

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*Abstract*

***BACKGROUND:*** Levodopa therapy currently remains the clinical method of choice for patients with Parkinson's disease. However, in the late stages of the disease, approximately 80% of patients receiving treatment developed levodopa-induced dyskinesia. The studied substances are derivatives of imidazole-4,5-dicarboxylic acid. Their pharmacological effect is produced due to interaction with the recognition site of NMDA receptor, which, together with their high efficiency, implies that they are safer than previously available drugs in this pharmacological group.

***AIM:*** To study the antidyskinetic effect of IEM2295 and IEM2296 derivatives of imidazole-4,5-dicarboxylic acid.

***MATERIALS AND METHODS:*** The model is based on the toxic effect of 6-hydroxydopamine on rat brain tissue. The first (control) group of rats received injections of only Levodopa and Benserazide, the second group received injections of Levodopa, Benserazide, and the test substance IEM2295, and the third group received injections of Levodopa, Benserazide and the test substance IEM2296. Each group was evaluated based on three criteria: motor function violations, limb dyskinesia, and axial and chewing dyskinesia. The severity of motor functions was graded on a scale of 0 to 4 points at 35, 70, 105, and 140 minutes after injection of the above substances, where 0 and 4 represent the absence and most pronounced degree of pathological movements, respectively.

***RESULTS:*** The result analysis showed that the greatest effect on reducing the severity of limb dyskinesia, axial dyskinesia, and chewing dyskinesia in rats was observed at 105 and 140 minutes after injections of the studied substances. Statistically significant differences between the control group and rats receiving injections of the studied substances were revealed at all the time points for limb dyskinesia; i.e., at 35, 105, and 140 minutes for axial dyskinesia and at 105 and 140 minutes for chewing dyskinesia.

***CONCLUSIONS:*** In the experimental model of parkinsonism, IEM2295 and IEM2296 show antiparkinsonian and antidyskinetic activity because they reduce the severity of motor function disorders in rats with levodopa-induced dyskinesia. The results indicate the prospects for continued development of these substances and further research for effective and safe antiparkinsonian agents among compounds of this class.

**Keywords:** 6-hydroxydopamine; dyskinesia; levodopa-induced complications; NMDA; Parkinson's disease; parkinsonism

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Научная статья

# Антидискинетическая активность новых производных имидазол-4,5-дикарбоновых кислот в экспериментальной модели паркинсонизма с введением 6-гидроксидофамина

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*Аннотация*

**Актуальность.** Заместительная терапия леводопой остается в настоящее время клиническим методом выбора для пациентов с болезнью Паркинсона, но примерно у 80 % пациентов, получающих лечение, развивается индуцированная леводопой дискинезия на поздних стадиях заболевания. Исследуемые вещества представляют собой производные имидазол-4,5-дикарбоновой кислоты. Их фармакологический эффект реализуется за счет взаимодействия с узнающим сайтом NMDA-рецептора, что, наряду с высокой эффективностью, позволяет предполагать их более высокую безопасность по сравнению с ранее существующими лекарственными средствами данной фармакологической группы.

**Цель** — изучение антидискинетического действия производных имидазол-4,5-дикарбоновой кислоты ИЭМ2295 и ИЭМ2296.

**Материалы и методы.** Модель основана на токсическом действии 6-гидроксидофамина на мозговую ткань крыс. 1-я (контрольная) группа крыс получала инъекции только леводопы и бенсеразида, 2-я группа — инъекции леводопы, бенсеразида и исследуемое вещество ИЭМ2295, 3-я группа — инъекции леводопы, бенсеразида и исследуемое вещество ИЭМ2296. Каждая группа оценивалась по 3 критериям нарушений двигательных функций: дискинезия конечностей, осевая дискинезия и жевательная дискинезия. Оценка выраженности двигательных функций проводилась по шкале от 0 до 4 баллов на 35, 70, 105 и 140-й минутах после введения вышеперечисленных веществ, где 0 — это отсутствие патологических движений, а 4 — наиболее выраженная степень патологических движений.

**Результаты.** Анализ результатов показал, что наибольший эффект снижения выраженности дискинезии конечностей, осевой дискинезии и жевательной дискинезии у крыс наблюдался на 105-й и 140-й минутах после введения исследуемых веществ. Статистически значимые различия между группой контроля и группой крыс с введением исследуемых веществ были выявлены на всех временных точках для дискинезии конечностей, на 35, 105 и 140-й минутах для осевой дискинезии, а также на 105-й и 140-й минутах для жевательной дискинезии.

**Заключение.** Производные имидазол-4,5-дикарбоновой кислоты ИЭМ2295 и ИЭМ2296 обладают противопаркинсонической и антидискинетической активностью, так как снижают выраженность нарушений двигательных функций у крыс с индуцированной леводопой дискинезией в условиях экспериментальной модели паркинсонизма. Полученные результаты свидетельствует о перспективности разработки данных веществ и дальнейшего поиска эффективных и безопасных противопаркинсонических средств среди соединений данного класса.

**Ключевые слова:** дискинезии; паркинсонизм; болезнь Паркинсона; NMDA; 6-гидроксидофамин; леводопа-индуцированные осложнения.

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# BACKGROUND

Parkinson's disease (PD) has a major effect on society. For reasons that are not yet fully understood, its incidence and prevalence have increased rapidly over the past two decades, probably due to rapid population aging. PD has a huge personal burden. Levodopa replacement therapy remains the current clinical treatment of choice for patients with PD; however, levodopa-induced dyskinesia (LID) occurs in approximately 80% of patients treated for advanced PD [1, 2]. The uniqueness of this degenerative disease is related to its chronicity, that is, it can persist for decades [3, 4].

Motor symptoms include bradykinesia, muscle rigidity, resting tremors, and postural instability. Patients with PD also experience various non-motor symptoms such as sleep disturbances, dementia, sensory impairment, and autonomic dysfunction [5–7].

The typical disease course is slow progression with increasing disability. PD also places a significant burden on caregivers and an increasing socio-economic burden on society [8, 9].

The marked heterogeneity of symptoms makes PD an ideal disease for evidence-based medicine, in which treatment methods such as pharmacotherapy, neurosurgery, and rehabilitation must be individually selected in accordance with the priorities and needs of each patient and, ultimately, with his/her genetic or other specific biological characteristics. However, this important advancement toward personalized medicine should not be overstated, as patients with PD also share common pathophysiological pathways, such as neuroinflammation or mitochondrial dysfunction; thus, certain treatments can benefit many people having diseases with seemingly different forms of development [6, 10].

## Role of glutamate and NMDA receptors in the pathogenesis and treatment of PD

Glutamate is the main excitatory neurotransmitter in the brain and is involved in the regulation of various neurological functions. NMDA receptors are a subtype of glutamate receptors that play important roles in synaptic plasticity, learning, and memory. In PD, growing evidence shows that the dysregulation of NMDA receptors may contribute to its pathophysiology [11, 12].

In PD, excitotoxicity is believed to be one of the main ways that involve the NMDA receptors. As dopamine levels decrease in the brain, glutamate release relatively increases, which can lead to the overstimulation of NMDA receptors and ultimately to neuronal damage. In addition to their role in excitotoxicity, NMDA receptors may be involved in the development of non-motor PD-related symptoms such as cognitive impairment and depression. Studies have shown that functions of NMDA receptors are altered in various brain regions in patients with PD and that these changes may contribute to the development of these non-motor symptoms [11, 13, 14].

While the role of glutamate in PD is still being investigated, targeting glutamate neurotransmission may represent a potentially new therapeutic approach for this disease. For example, drugs that modulate glutamate receptors or reduce glutamate release have shown promising results in preclinical studies and clinical trials [15, 16].

## Effect of levodopa on the development of dyskinesias

Levodopa, prescribed in combination with carbidopa, is the most commonly used drug for PD treatment. As the disease progresses, nearly all patients with PD undergo dopamine replacement therapy using levodopa. Although levodopa is the gold standard in the treatment of PD and may alleviate PD symptoms, it has side effects with long-term use [17, 18].

LID develops in approximately 80% of patients treated for advanced PD. A deeper understanding of the pathological mechanisms of LID and possible ways to compensate for them would substantially improve the treatment outcomes of patients with PD and reduce the complexity of drug use and side effects, thereby improving the quality of life and prolonging the life cycle. In Russia, only one noncompetitive NMDA blocker (amantadine) is registered for the treatment of PD. Various NMDA receptor antagonists are undergoing preclinical and clinical trials. Currently, amantadine and other NMDA receptor ligands under evaluation are the most relevant methods to eliminate LID [1, 2, 19, 20].

*The study aimed* to analyze the antidyskinetic effect of new ligands of the glutamate NMDA receptor complex, namely, 1,2-substituted imidazole-4,5-dicarboxylic acids (IEM2295 and IEM2296). Based on the results of previous studies on the activity of imidazole dicarboxylic acid derivatives and given the similarity in the pharmacological action of amantadine and the studied compounds, IEM2295 and IEM2296 were assumed to demonstrate pronounced antidyskinetic activity [21–23].

# MATERIALS AND METHODS

A total of 25 rats were examined, and some were excluded from the study during the experiment. The model was based on the toxic effect of 6-hydroxydopamine (6-HODA) on the rat brain tissue [24, 25]. Given that 6-HODA penetrates the blood–brain barrier poorly, the solution was injected directly into the brain tissue through a previously provided trepanation access; the surgical intervention was performed under aseptic conditions with preliminary anesthesia. Thirty minutes before the administration of 6-HODA, desipramine was injected intraperitoneally to enhance the selective toxic effect on dopamine neurons. The 6-HODA solution was injected unilaterally into the compact area of the substantia nigra according to the coordinates of the stereotaxic atlas. The

neurotoxin was injected using a Hamilton syringe at a rate of 1 μL/min.

Three weeks after surgery, the animals were placed in polycarbonate boxes, and to assess the severity of the damaging effect of the neurotoxin, d-amphetamine sulfate was administered once. After 30 min, ipsilateral movements were recorded (i.e., symptoms of damage to the cells of the substantia nigra), and the rats that demonstrated symptoms were included in the experiment. The remaining animals were divided into three groups of six animals each. Group 1 (control) received injections of only levodopa and benserazide, group 2 received injections of levodopa, benserazide, and IEM2295 at (test substance) a dose of 30 mg/kg, and group 3 received injections of levodopa, benserazide, and IEM2296 (test substance) at a dose of 20 mg/kg. The doses of the studied compounds were selected from those that demonstrated the highest antiparkinsonian activity in previous experiments.

Each group was assessed according to the three criteria for motor dysfunction, namely, limb dyskinesia, axial dyskinesia, and masticatory dyskinesia.

The severity of motor functions was assessed on a scale ranging from 0 to 4 points 35, 70, 105, and 140 min after the administration of the above substances, where 0 was the absence of pathological movements, and 4 indicated the most pronounced degree of pathological movements.

Results were statistically processed using MS Excel 2010 and BioStat 2009. The normality of data distribution was determined using the Shapiro–Wilk test. The significance of the differences in values between groups was determined using the Newman–Keuls rank test.

## RESULTS

When assessing limb dyskinesia (Fig. 1), statistically significant differences were revealed between the control group and the IEM2295 group at the 70$^{th}$ ($p$ = 0.028846), 105$^{th}$ ($p$ = 0.000203), and 140$^{th}$ ($p$ = 0.000195) minute and between the control group and the IEM2296 group at the 70$^{th}$ ($p$ = 0.039564), 105$^{th}$ ($p$ = 0.000208), and 140$^{th}$ ($p$ = 0.000173) minute.

In the assessment of axial dyskinesia (Fig. 2), statistically significant differences were found between the control group and group 2 at the 35$^{th}$ ($p$ = 0.027807), 105$^{th}$ ($p$ = 0.005529), and 140$^{th}$ ($p$ = 0.001275) minute and between the control group and group 3 at the 105$^{th}$ ($p$ = 0.019900) and 140$^{th}$ ($p$ = 0.001174) minute.

When assessing masticatory dyskinesia (Fig. 3), statistically significant differences were found between the control group and group 2 at the 105$^{th}$ ($p$ = 0.009257) and 140$^{th}$ ($p$ = 0.000461) minute and between the control group and group 3 at the 105$^{th}$ ($p$ = 0.020323) and 140$^{th}$ ($p$ = 0.000266) minute.

In other cases, no statistically significant differences were noted.

## DISCUSSION

The results of the experiment indicated that the new ligands of the glutamate NMDA receptor complex, namely, IEM2295 and IEM2296, demonstrated antiparkinsonian and antidyskinetic activities because they reduce the severity of motor dysfunction in rats with LID in an experimental model of parkinsonism.

Analysis of the results revealed that the greatest effect on reducing the severity of limb dyskinesia, axial dyskinesia, and masticatory dyskinesia in rats was registered at the 105$^{th}$ and 140$^{th}$ minute after the administration of the test substances. Statistically significant differences between the control group and the test group were detected at all time points for limb dyskinesia; at the 35$^{th}$, 105$^{th}$, and 140$^{th}$ minute for axial dyskinesia; and at the 105$^{th}$ and 140$^{th}$ minute for masticatory dyskinesia.

The main hypothesis is that the new ligands of the glutamate NMDA receptor complex, namely, 1,2-substituted imidazole-4,5-dicarboxylic acids (IEM2295 and IEM2296),

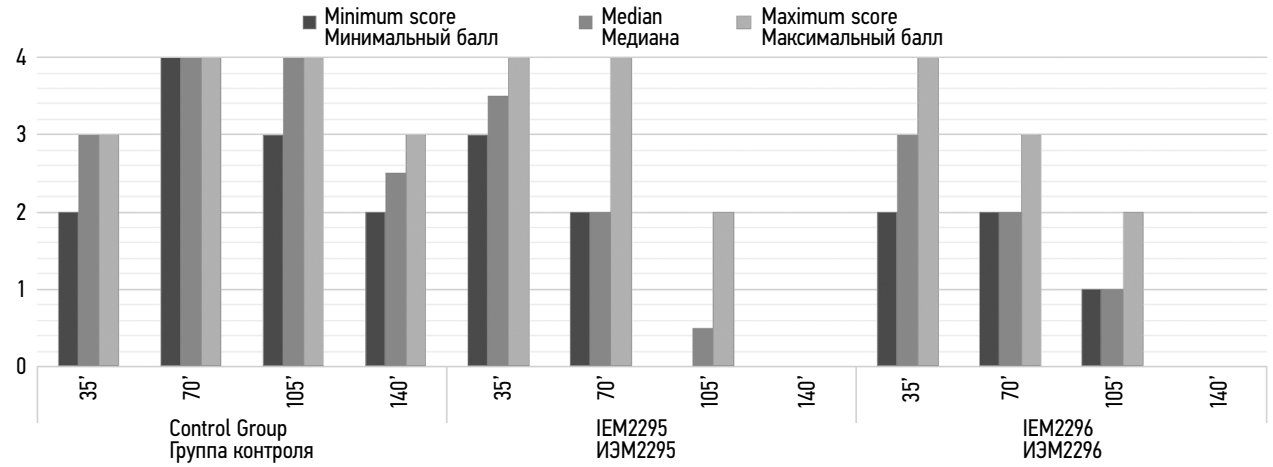


**Fig. 1.** Results of the assessment of limb dyskinesia

**Рис. 1.** Результаты оценки дискинезии конечностей

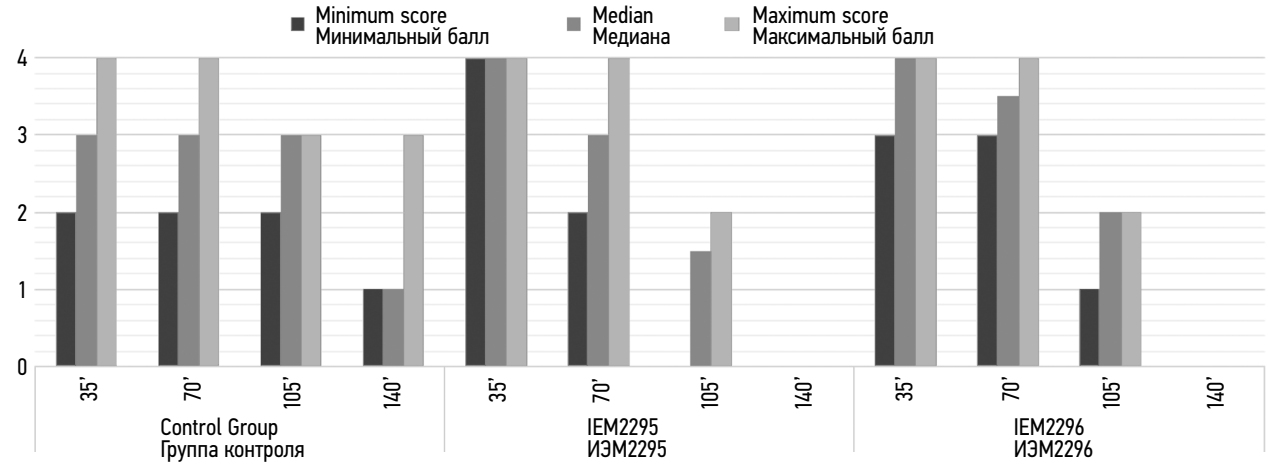


**Fig. 2.** Results of the assessment of axial dyskinesia

**Рис. 2.** Результаты оценки осевой дискинезии

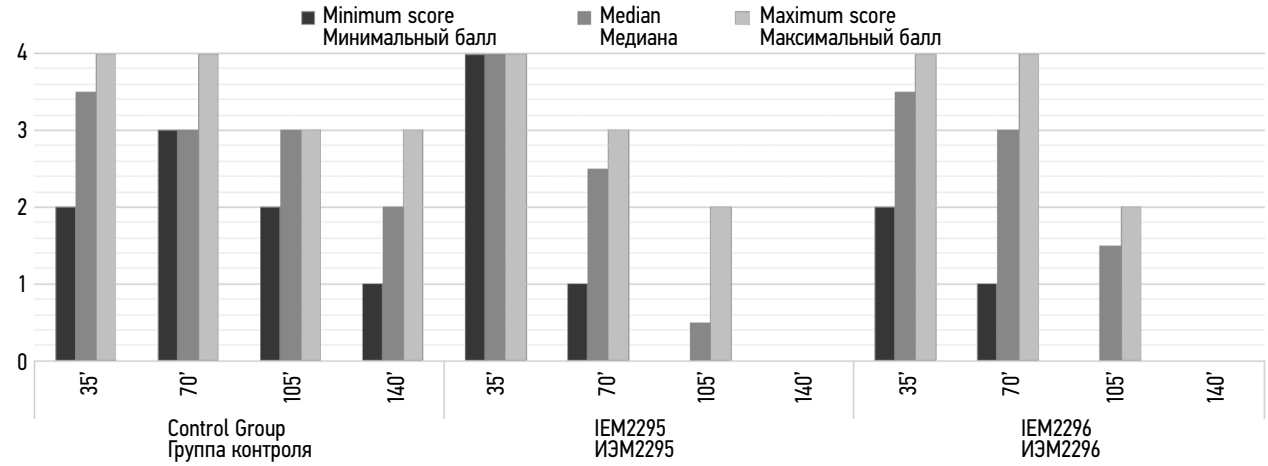


**Fig. 3.** Results of the assessment of chewing dyskinesia

**Рис. 3.** Результаты оценки жевательной дискинезии

have antidyskinetic activity because of their noncompetitive antagonism ability, that is, NMDA-blocking effect when interaction with hyperactive glutamate receptors of the striatum helps dispose of peak-dose dyskinesias [18, 26–28].

## CONCLUSION

The studied compounds demonstrated a pronounced antidyskinetic effect on the model with the administration of 6-HODA. Considering their effect on the glutamatergic system, the most effective method might be the combination with other antiparkinsonian drugs, which will allow interaction with all pathogenetic links of PD [29].

The results indicate the prospects for the development of these substances and further search for effective and safe antiparkinsonian drugs in the range of compounds of this class.

## ADDITIONAL INFORMATION

**Authors contribution.** Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. The contribution of each author: V.D. Dergachev, E.E. Yakovleva, M.A. Brusina, E.R. Bychkov — manuscript drafting, writing and pilot data analyses; L.B. Piotrovskiy, P.D. Shabanov — general concept discussion.

**Competing interests.** The authors declare that they have no competing interests.

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Вклад каждого автора: В.Д. Дергачев, Е.Е. Яковлева, М.А. Брусина, Е.Р. Бычков — написание статьи, анализ данных; Л.Б. Пиотровский, П.Д. Шабанов — разработка общей концепции.

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