# PHARMACOLOGY AND TOXICOLOGY

# Study of Antiparkinsonic Activity of Panavir on a Model of Parkinson Syndrome Induced by Systemic Administration of MPTP to Outbred Rats and C57Bl/6 Mice

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 140, No. 7, pp. 65-67, July, 2005
Original article submitted December 3, 2004

The effect of panavir on Parkinson's syndrome induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was studied in C57Bl/6 mice and outbred albino rats. Two injections of panavir significantly reduced the severity of oligokinesia and autonomic manifestations of experimentally induced Parkinson's syndrome.

**Key Words:** *Parkinson's syndrome; MPTP; neurotoxin; dopamine*

Parkinson's syndrome (PS) is a characteristic sign of many diseases of different etiology: primary parkinsonism, including Parkinson's disease, secondary parkinsonism (vascular, traumatic, infectious, toxic drug-induced), and of some forms of multisystemic degeneration. PS is characterized by a classical triad of symptoms: tremor, rigidity, and oligokinesia [1,6]. Despite the differences in the etiology of PS, the main pathogenetic components in the mechanism of its development are dopamine deficiency and hyperactivation of cholin- and glutamatergic neurons [4-6].

The model of PS induced by injection of neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is most adequate, because MPTP selectively damaged dopaminergic neurons of the substantia nigra. Under the effect of monoamine oxidase B (MAO-B) MPTP in astrocytes transforms into 1-methyl-4-phenylpyridine, which enter dopaminergic neurons via dopamine transporter and causes energy deficiency by inhibiting complex I in the mitochondrial respiratory chain [6,8].

The group of antiparkinsonian drugs includes agents with different mechanisms of action aimed at the main components in PS pathogenesis. Drugs improving dopaminergic transmission are most important: L-DOPA and its derivatives, dopamine receptor agonists (bromocryptine, lisuride, pergolide), and MAO-B inhibitors (selegiline, jumex) [1,6]. Cholinolytics (cyclodol, dipyridine, *etc.*) are used as monotherapy at the early stages and in combined therapy [6].

Adamantane derivatives, stimulating dopaminergic transmission and limiting the formation of free radicals and possessing antiviral and immunotropic activities, are also used in the treatment of PS [2,6,7].

Panavir, a new drug used in therapy of neurological complications of tick-borne encephalitis (reduced reflexes, nystagmus, anisoreflexia, painful sites of craniocerebral nerve endings), exhibited a pronounced cytoprotective effect under conditions of experimental *in vitro* infection [3]. We studied antiparkinsonic effect of panavir on a model of PS induced by MPTP treatment in mice and rats.

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0007-4888/05/1401-0055 

## MATERIALS AND METHODS

Experiments were carried out on 43 outbred male rats (380-420 g) and 60 male C57Bl/6 mice (18-20 g) from Stolbovaya Breeding Center, Russian Academy of Medical Sciences. The animals were kept under standard conditions at natural illumination. Behavioral experiments were carried out at 10.00-14.00.

Parkinson's syndrome was induced by administration of MPTP (Institute of Pharmacology) to rats and mice in doses of 40 and 30 mg/kg, respectively.

Panavir (Flora&Fauna+) is a 0.004% isotonic solution in 5-ml ampoules; 1 ml solution contains 0.04 mg active substance. Panavir composition (determined by enzymatic hydrolysis with subsequent gas liquid chromatography) is as follows: 1.5% xylose, 6% rhamnose, 9% arabinose, 38.5% glucose, 14.5% galactose, 2.5% mannose, and 3.5% uronic acids. Panavir was injected intraperitoneally twice 24 and 1 h before MPTP (mice: 0.016 mg, 0.4 ml; rats: 0.1 mg, 2.5 ml).

Animals of control group 1 (passive control) received 3 injections of saline: first 2 injections at 24-h interval, third injection 1 h after the second injection. Animals of control group 2 (active control) received 2 injections of saline at 24-h interval and MPTP 1 h after the second injection of saline. Experimental animals (group 3) received 2 injections of panavir at 24-h interval and MPTP 1 h after the second injection.

Oligokinesia was evaluated 1.5 h after injection of MPTP by the locomotor activity in an Opto-Varimex device (mice) and by the orientation and exploratory reaction (OER) in the open field test [5]. The presence (absence) of tremor and rigidity was recorded in mice and rats immediately after injection of the neurotoxin. Piloerection, salivation, Straube syndrome, stupor, and catalepsy were recorded in rats. Panavir efficiency was evaluated by its capacity to reduce the percentage of animals with signs of PS.

The results were processed using Student's unpaired *t* test (Biostatistics-III software), Wilcoxon—Mann—Whitney test, and method for evaluation of selective shares of variants (Biostadt).

## RESULTS

Tremor and rigidity developed in rats directly after MPTP injection and were characteristic of the majority of animals. Autonomic disorders (salivation, piloerection), stupor, catalepsy, manifestations of Straube syndrome were observed (Table 1). Panavir treatment appreciably reduced the percentage of animals with rigidity, piloerection, Straube syndrome, stupor, and catalepsy, but did not influence the severity of tremor. Open field test carried out 1.5 h after MPTP injection showed a 2.5-fold reduction of OER in comparison

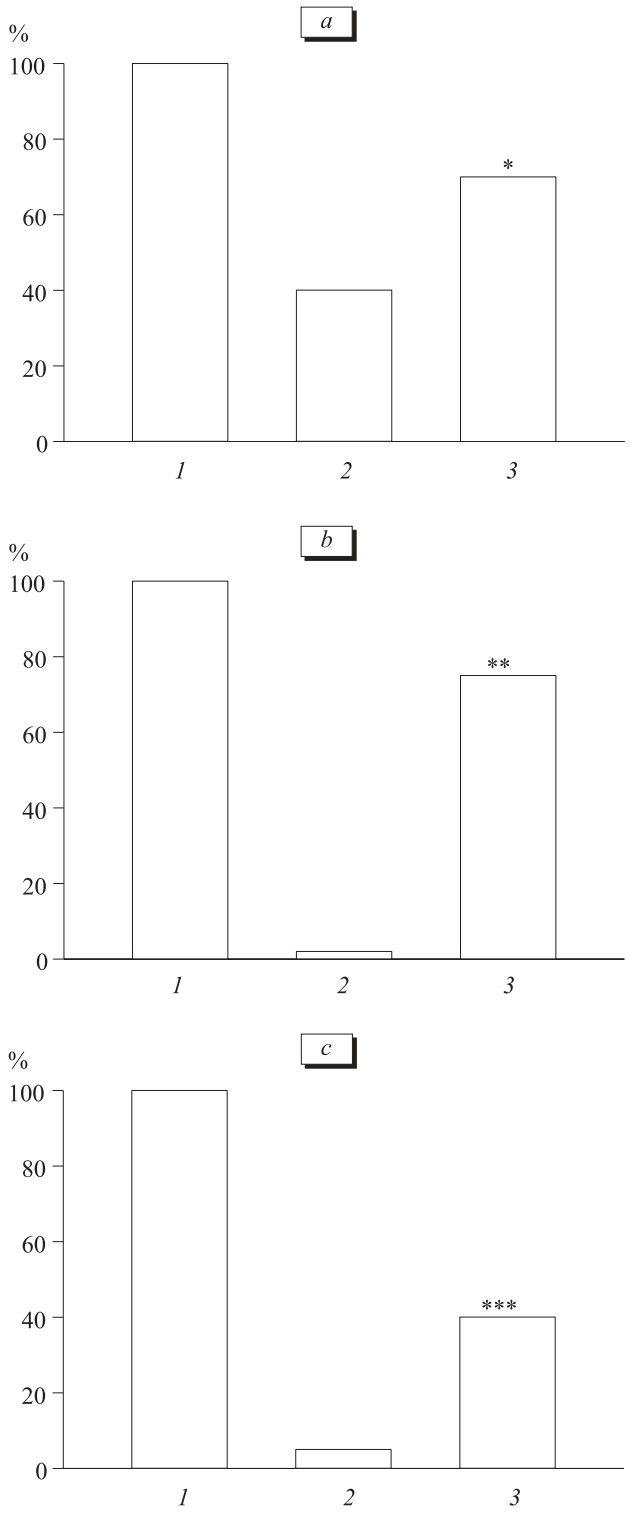


**Fig. 1.** Effect of panavir on MPTP-induced oligokinesia in rats (*a*) and mice (*b*, *c*). *1*) control (6 rats, 10 mice); *2*) MPTP (40 mg/kg for rats, $n$=6, and 30 mg/kg for mice, $n$=10); *3*) two injections of panavir (2.5 ml for rats, $n$=6, and 0.4 ml for mice, $n$=10) 24 and 1 h before MPTP injection. Ordinate: changed activity of animals compared to passive control group, taken for 100%. *$p$<0.05 (Wilcoxon—Mann—Whtney test), **$p$<0.01 (method for evaluation of selective shares of variants), ***$p$<0.001 (Student's unpaired *t* test) compared to MPTP.

**TABLE 1.** Effect of Panavir on MPTP-Induced PS in Rats

| Group | MPTP-induced PS in rats, % | | | | | |
|---|---|---|---|---|---|---|
| | tremor | rigidity | piloerection | Straube syndrome | stupor | catalepsy |
| Control ($n$=10) | 0 | 0 | 0 | 0 | 0 | 0 |
| Saline+MTPT ($n$=27) | 94.4 | 94.4 | 96.3 | 94.4 | 66.7 | 63.0 |
| Panavir+MPTP ($n$=6) | 91.7 | 58.3* | 58.3* | 41.7* | 0** | 0** |

**Note.** *$p \leq 0.05$, **$p \leq 0.01$ compared to MPTP (according to method for evaluation for selective shares of variants).

with group 1. Treatment with panavir 1.8-fold increased OER in comparison with group 2 (Fig. 1, *a*).

Similarly to rats, tremor and rigidity were observed in mice directly after injection of MPTP. Panavir virtually did not modify these manifestations of PS. Locomotor activity of group 2 animals was virtually completely suppressed. Panavir significantly increased motor activity in mice (75% of motor activity in group 1, Fig. 1, *b*). Injection of MPTP significantly reduced OER in the open field test in comparison with group 1 mice (Fig. 1, *c*). Panavir treatment 10-fold increased OER in experimental animals (39.3% of OER level in group 1).

The results suggest that panavir exhibits antiparkinsonic activity, which manifested in reduction of oligokinesia in C57Bl/6 mice and outbred rats with MPTP-induced PS. In rats antiparkinsonic effect of the drug manifested also in reduction of rigidity and other PS symptoms, such as piloerection, Straube syndrome, stupor, and catalepsy. Panavir capacity to attenuate PS symptoms under conditions of simulation of selective death of substantia nigra dopaminergic neurons indicates its central mechanisms, linked with compensation for dopaminergic deficiency of the nigrostriate system of the brain.

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