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THE EFFECT OF PIR-12 COMPOUND ON SURVIVAL AND NEUROLOGICAL DEFICITS IN EXPERIMENTAL GLOBAL CEREBRAL ISCHEMIA IN RATS

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ABSTRACT — This study was aimed to assess the effect of a new pyrimidine derivative (PIR-12 50 mg/kg) on survival and neurological deficits in rat global brain ischemia. It has been confirmed that the investigated compound PIR-12 contributes to an increase in survival up to 80% and a decrease in neurological status by 73,3% compared to the control group of animals and exceeds the strength of the effect of the reference drug Cavinton by 30% and 22,48%, respectively.

KEYWORDS — brain ischemia, the survival rate, neurological deficit, derivatives of pyrimidine.

INTRODUCTION

Currently, brain ischemia has remained one of the most common pathologies in modern society [1]. With cerebrovascular brain damage, first of all, neurological disorders occur, and therefore effective and timely therapy is a key link in the treatment of this pathology. Pyrimidine derivatives have been found to possess pronounced anti-inflammatory [2], anti-aggregation [3], and endothelioprotective [4] properties, therefore, other types of pharmacological activity, including cerebroprotective activity, can be assumed for this group of substances.

Objective:

To study the effect of PIR-12 compound on survival and neurological deficits in experimental global cerebral ischemia in rats.

MATERIALS AND METHODS

The study was conducted in accordance with the "Guidelines for Preclinical Trials of Drug Products" ed. by A.N. Mironov (a 2012 edition.) [5]. The animals were maintained in compliance with current best practices and standards of care in laboratory animals. The experiment was performed on 40 male Wistar rats m=220–240 g, divided into 4 groups (n=10). Rats were kept on a standard vivarium diet, with a natural succession of light and darkness. The first group was represented by falsely operated rats (FO), the second one — by negative control animals (NC). The both groups received an intraperitoneal suspension of Tween-80 in purified water. The third and fourth groups received reference drugs: Cavinton (3,2 mg/kg) [6]. The fourth group was administered the pyrimidine derivative PIR-12 (50 mg/kg) [7]. The second and subsequent groups were simulated global brain ischemia by bilateral occlusion of the common carotid arteries (under chloral hydrate anesthesia 350 mg/kg) [8, 9]. All objects were injected intraperitoneally for three days before the operation. A day after modeling the pathology, the survival rate of animals and their neurological deficit were evaluated on the McGraw scale. All findings were processed by means of variation statistics methods using the STATISTICA 6.0 software. The normality of distribution was assessed by the Shapiro-Wilk test. In the case of a normal distribution of the data, a parametric t-test was applied. In the case of abnormal distribution of the data, the statistical processing was performed using the Mann-Whitney U-test. The difference was considered significant at the significance level of more than 95% ($p<0,05$).

RESULTS

Irreversible occlusion of the common carotid arteries led to the death of 70% of the negative control group (NC) rats, while no mortality was observed in the falsely operated animals (Fig. 1). In the surviving individuals of the NC group who did not receive pharmacological support, the degree of neurological disorders reached 7,5±0,29 points (Fig. 2), which was manifested in lethargy, slowness and Manege of movements, one- and two-sided ptosis of the eyelids, paresis of the limbs, and in some cases paralysis. Against the background of prophylactic administration of Cavinton, the mortality rate of animals reached 40%, and the neurological deficit on the McGraw scale was 2,58±0,27 points, which is 65,6% less than the same

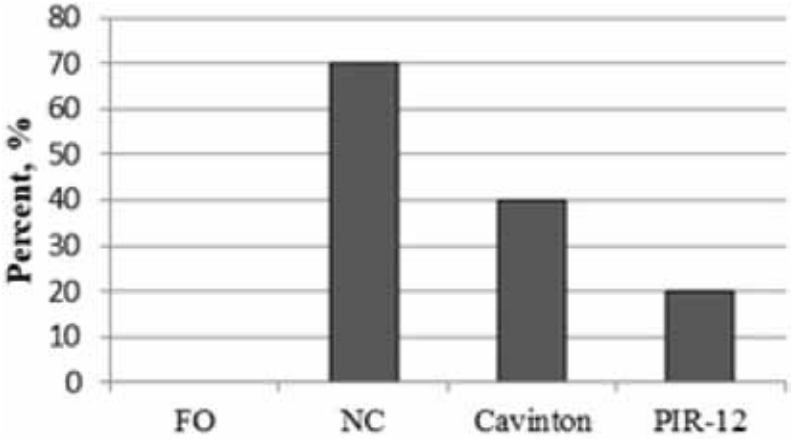

Fig. 1. *Assessment of the effect of PIR-12 and Cavinton compounds on the mortality rate of global cerebral ischemia in rats.*
Note: *FO — false-operated rats ; NC — negative control rats; Cavinton — a group rats treated with Cavinton; PIR-12 — a group of rats treated with PIR-12.*

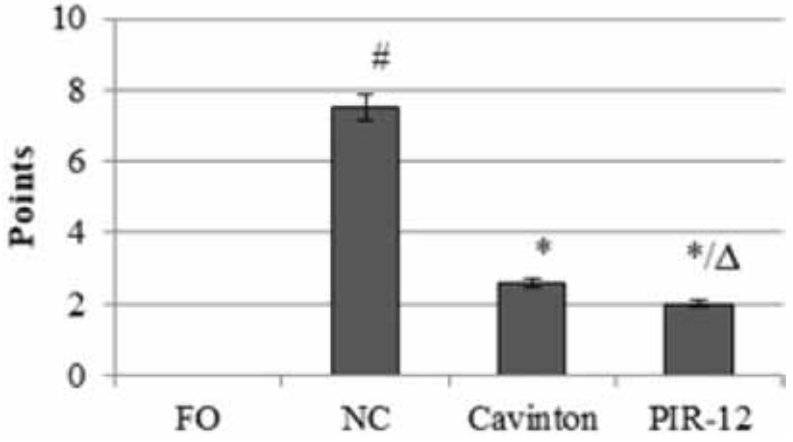

Fig. 2. *Assessment of the effect of PIR-12 and Cavinton on the severity of neurological deficits in the conditions of global cerebral ischemia in rats.*
Note: *FO — false-operated rats ; NC — negative control rats; Cavinton — a group of rats treated with Cavinton; PIR-12 — a group of rats treated with PIR-12; # — statistically significant as compared to the FO rats (p<0,05); * — statistically significant as compared to the NC rats (p<0,05); Δ — statistically significant as compared to rats treated with Cavinton (p<0,05).*

indicator of the NC group of rats (p<0,05). Under conditions of cerebral ischemia, the mortality rate of rats treated with intraperitoneal PIR-12 compound was 20%, while the indicators of neurological deficit decreased as much as possible relative to untreated rats by 73,3% (p<0,05). At the same time, the neurological status of PIR-12 animals was 22,48% lower than that of Cavinton rats (p<0,05), which was statistically significant.

CONCLUSION

In the experimentally simulated cerebrovascular insufficiency, a pyrimidine derivative under the laboratory code PIR-12 allowed to compensate for survival and reduce neurological deficit, and showed an effect which exceeded in its strength that of the non-targeted drug Cavinton.

REFERENCES

1. **Cheng Y-C., Sheen J-M., Hu W.L., Hung Y-C.** Polyphenols and Oxidative Stress in Atherosclerosis-Related Ischemic Heart Disease and Stroke //Oxidative Medicine and Cellular Longevity. – 2017. – Vol. 2017. – P. 8526438. DOI: 10.1155/2017/8526438
2. **Sochnev V. S., Kodonidi I. P., Bandura A.V., Smirnova L. P., Ivchenko A.V., Shatokhin S. S., Filimonov Yu. D., Kodonidi M. I.** Molecular design and synthesis of new 2-vinylenesubstituted derivatives of 1H-pyrimidine-4-one with predicted anti-inflammatory activity // Modern problems of science and education. – 2015. – No 2–2. (In Russ.)
3. **Voronkov A.V., Kodonidi I. P., Mamleev A.V., Sochnev V. S., Glushko A. A.** Search and study of endothelioprotective activity of new 2-styryl derivatives of pyrimidin4(1H)-on against the background of modeling of sex hormone insufficiency // Modern problems of science and education. – 2015. – No 5. (In Russ.)

4. **Voronkov A.V., Mamleev A.V., Pozdnyakov D. I.** Study of the effect of pyrimidine–4(1H)-one styryl derivatives on the state of antithrombotic potential, against the background of experimentally induced insufficiency of sex hormones // Journal of scientific articles "Health and education in the XXI century". – 2016. – Vol. 18, No. 2. – Pp. 603–608. (In Russ.)

5. **Mironov A.N.** The guidelines for preclinical studies of pharmaceuticals. Part one. – M.: Grif and K, 2012. – 944 p. (In Russ.)

6. **Nazarova L.E., Dyakova I.N.** Influence of ferulic acid on the necrosis zone resulting from occlusion of the middle cerebral artery //medical Bulletin of Bashkortostan 2011. No. 3. P. 133–135. (In Russ.)

7. **Voronkov A.V., Shabanova N.B., Voronkova M.P., Lysenko T.A.** Study of cerebrotropic dose-dependent effect of pyrimidine derivative under pir-9 code against the background of experimental cerebral ischemia in rats. Pharmacy & Pharmacology. 2018;6(6):548–567. (In Russ.) DOI: 10.19163/2307-9266-2018-6-6-548-567

8. **Yamamoto M., Shima T., Uozumi T., Sogabe T., Yamada K., Kawasaki T.** A possible role of lipid peroxidation in cellular damages caused by cerebral ischemia and the protective effect of alpha-tocopherol administration // Stroke. – 1983. – Vol 14, №6. – P. 977–982. DOI: 10.1161/01.STR.14.6.977

9. **Ghanbarabadi M., Falanji F., Rad A., Sharahi N.C., Amoueian S., Amin M., Molavi M., Amin B.** Neuroprotective effects of clavulanic acid following permanent bilateral common carotid artery occlusion in rats // Drug Development Research. – 2019. – Vol. 80. – №. 8. – P. 1110-1119. DOI: 10.1002/ddr.21595