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INFLUENCE OF A NEW PYRIMIDINE DERIVATIVE PIR-9 ON THE ACTIVITY OF VON WILLEBRAND FACTOR IN FOCAL CEREBRAL ISCHEMIA IN RATS

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ABSTRACT — A study was conducted to assess the effect of a new pyrimidine derivative PIR-9 (50 mg/kg) on the activity of von Willebrand factor in the conditions of focal brain ischemia in rats. It was confirmed that the studied compound PIR-9 contributes to a decrease in the activity of von Willebrand factor by 14,1% (p<0,05) compared to the group of negative control rats. PIR-9 exceeds the comparison drug Cavinton by 10,9% in strength of effect (p<0,05) comparable to sulodexide.

KEYWORDS — brain ischemia, cerebral ischemia, pyrimidine derivatives, von Willebrand factor, endothelial dysfunction.

INTRODUCTION

Disorders of cerebral hemodynamics currently remain one of the leading causes of death and disability in the working population [1], while vascular endothelium plays an important role in their development [2]. Von Willebrand factor (VWF) is a specific marker of endothelial dysfunction, an increase in the activity of which in combination with an increase in the aggregation ability of platelets indicates a violation of the functioning of the vascular endothelium [3]. Thus, agents that restore pathologically increased activity of von Willebrand factor in the post-ischemic period can be considered as potential cerebroprotectors. Previous studies indicate the presence of cerebrotropic properties in pyrimidine derivatives [4], which makes it interesting to study the effect of these compounds on VWF activity in conditions of acute cerebral circulation disorders.

Objective

To study the effect of a new pyrimidine derivative PIR-9 on the activity of von Willebrand factor in the conditions of focal 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 experiment was performed on 50 male Wistar rats (m = 200–220 g), divided into 5 groups (n=10)). Rats were kept on a standard vivarium diet, with a natural succession of light and darkness. The first group — falsely operated animals (FO), the second — negative control group (NC), the third and fourth — rats who were administered the comparison drug Cavinton (3,2 mg/kg) and Sulodexide (30 URL/kg (units the release of lipoprotein lipase)), respectively [6, 7]. The fifth group of animals received the studied compound PIR-9 (50 mg/kg) [8]. The second and subsequent groups modeled focal cerebral ischemia, by occlusion of the left middle cerebral artery (under chloral hydrate anesthesia, 350 mg/kg) [9]. The studied objects were introduced immediately after the operation and then for 3 days. The activity of the von Willebrand factor (VWF) was determined by agglutination method using a set of reagents of the NGO "RENAM". 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

As can be seen from figure 1, the concentration of VWF in the group of animals with the simulated pathology that were not subjected to therapy was 133,5±2,3%, which was 37,87% (p<0,05) significantly higher than that of false-operated rats (96,83±2,46%). The introduction of Cavinton did not significantly

reduce the level of Willebrand factor relative to untreated rats, while another comparison drug — Sulodexide led to a decrease in the studied indicator by 19,9% (p<0,05) (at the same time, significantly higher than the FO value of the rat group). It is worth noting that the level of VWF against the background of the introduction of the comparison drug sulodexide was also significantly lower than this value in the Cavinton group of rats by 16,9% (p<0,05). Against the background of PIR-9 therapy, a decrease in VWF was also observed, so this indicator was 114,7±2,8 %, which in turn differed by 14,1% (p<0,05) from the identical value of the group of rats that did not receive pharmacological support and by 11% (p<0,05) in comparison with the group of rats that were administered Cavinton. There were no statistically significant differences between the groups receiving the experimental substance PIR-9 and the comparison drug Sulodexide.

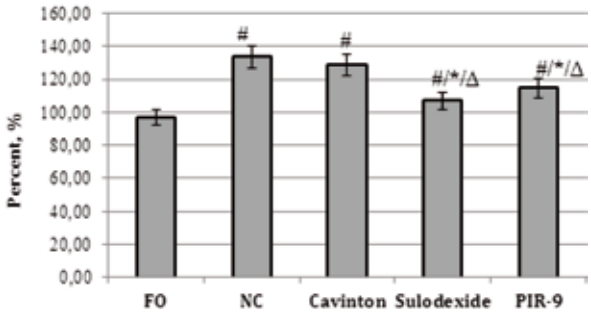

Fig. 1. *Assessment of the effect of PIR-9 compound and reference drugs on the activity of von Willebrand factor under conditions of focal cerebral ischemia in rats*

Note: *FO — a group of false-operated rats; NC group of rats negative control; NC — negative control rats; Cavinton — a group rats treated with Cavinton; Sulodexide — a group rats treated with Sulodexide; PIR-9 — a group of rats treated with PIR-9; # — 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).*

CONCLUSION

The introduction of a new pyrimidine derivative under the code PIR-9 (50 mg/kg) significantly reduced the pathologically overestimated activity of von Willebrand factor by 14,1% (p<0,05) relative to the group of negative control rats and by 10,9% (p<0,05) in comparison with animals receiving Cavinton, which may indicate a decrease in platelet adhesion against the background of receiving this compound by rats. By the strength of its effect, the PIR-9 compound surpassed the comparison drug Cavinton (3,2 mg/kg) and was comparable to sulodexide (30 URL/kg), this fact is an important link in the correction of endothelial dysfunction resulting from acute cerebral circulation disorders. Thus, the pyrimidine derivative under the code PIR-9 is a promising object for further study and correction of ischemic brain injuries.

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