EFFECT OF PICAMILON ON THE CEREBRAL CORTICAL BLOOD SUPPLY AND MICROCIRCULATION IN THE PIAL ARTERIOLAR SYSTEM

R. S. Mirzoyan, T. S. Gan'shina,
M. Yu. Kosoi, V. V. Aleksandrin,
and P. N. Aleksandrov

UDC 615.225.2.015.4:616.831-005].076.9

KEY WORDS: cerebral circulation; picamilon; microcirculation

A new cerebrovascular drug picamilon (the sodium salt of N-nicotinoyl-γ-aminobutyric acid) has been synthesized by the Institute of Pharmacology, Academy of Medical Sciences of the USSR, and the "Vitaminy" Scientific-Industrial Association of the Ministry of the Medical and Biological Industry, and has been approved for wide medical use. It was shown previously that picamilon significantly increases the cerebral blood flow in conscious animals, has a depressant effect on neurogenic spasms of cerebral vessels, and restores the initial state of the cerebral hemodynamics when disturbed by preliminary injection of serotonin.

The aim of this investigation was to study the effect of picamilon on the local blood flow in the cerebral cortex and on the state of pial arteries of different diameter.

EXPERIMENTAL METHOD

Experiments were carried out on 44 noninbred male rats weighing 250-300 g and on six rabbits weighing 2.5-3.5 kg. The local cerebral blood flow was recorded by the hydrogen clearance method [3] on an LP-7e polarograph (Czechoslovakia). For this purpose, an operation was performed 7-14 days before the experiment to implant working platinum electrodes into the rats under general anesthesia (hexobarbital 150 mg/kg, intraperitoneally) and into rabbits under local anesthesia (2% procaine solution). The electrodes were made from platinum wire 0.3 mm in diameter, covered with insulation, but leaving the electrode tip bare. The platinum electrodes were inserted stereotaxically into the parietal cortex through holes drilled in the skull of the previously scalped animals: in rats to a depth of 1.5-1.8 mm and in rabbits to a depth of 4-5 mm from the surface of the skull. The electrodes were then fixed with quick-hardening plastic (Noracryl). A chlorided silver clip, applied to the ear, was used as comparison electrode for the rats, and a rectal carbon electrode served the same purpose for the rabbits. The diameter of the pial arterioles was studied in rats under general anesthesia (chloral hydrate, 60 mg/kg intramuscularly). The animals were placed in a frame, in which the head was securely fixed. The right half of the skull was trephined in the region of the parietal bone (diameter of the burr-hole 3 × 4 mm), so that branches of the middle cerebral artery could be kept under observation. In experiments in which the drug was injected intravenously, biomicroscopy of the pial vessels was carried out through the dura mater, using a ×10 contact objective. The total magnification was ×50. Bicarbonate-buffered physiological saline (pH 7.4, temperature 37°C) was used as the immersion medium. In the experiments with application of the drug, the dura mater was removed. The blood vessels were photographed 40 min after the end of dissection by means of a "Praktika" camera, on black and white KN-3 motion picture negative film (sensitivity 90 units). The diameter of the vessels was measured on the negatives by means of a "Mikrofoto" apparatus, with graduated scale (in μ). To assess the state of reactivity of the vascular bed, testing was done with a gas mixture containing 8% CO_2. Picamilon was injected intravenously and intraperitoneally into the rats and administered perorally in a dose of 20-50 mg/kg; it was injected intravenously into rabbits in a dose of 10 mg/kg. The animals were killed with a mixture of urethane and chloralase or with ether.

Laboratory of Pharmacology of Cerebrovascular Disorders, Research Institute of Pharmacology, Academy of Medical Sciences of the USSR. Laboratory of General Pathology of the Microcirculation, Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 107, No. 5, pp. 581-582, May, 1989. Original article submitted May 5, 1988.

 0007-4888/89/0005-0668$12.50

TABLE 1. Increase in Local Cerebral Blood Flow in Parietal Cortex of Waking Rats and Rabbits under the Influence of Picamilon (in % of initial level, with standard error of mean and confidence limits)

Rats (50 mg/kg), intraperitoneally	Perorally	Rabbits (10 mg/kg), intravenously
12	14	24
23	47	19
79	68	12
81	14	50
61	22	14
21	29	67
78	—	—
58	—	—
52±10,1 (33—71)	32±8,7 (14—50)	31±9,1 (13—49)

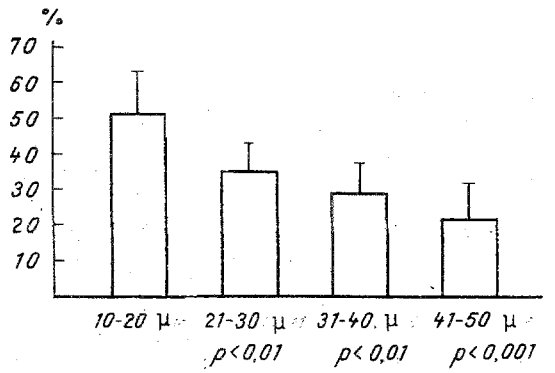

Fig. 1. Change in diameter of arterioles under influence of picamilon (0.2 ml of 5% solution) when applied to pial network in rats. Abscissa, groups of arterioles, depending on diameter (in μ); ordinate, diameter of vessels (in % of initial value).

EXPERIMENTAL RESULTS

The experiments showed that picamilon in a dose of 50 mg/kg, injected intraperitoneally, increased the cerebral blood flow in conscious rats on average by 52 ± 10.1% (Table 1). An increase in the cortical blood flow was observed as early as 5-10 min after injection of picamilon. In most experiments the maximal increase of blood flow occurred 40-45 min after injection of the drug. The initial level of the blood flow was restored after 60-70 min. When administered perorally, picamilon in the same dose increased the local cerebral blood flow on average by 32 ± 8.7%. The maximal effect of picamilon in these experiments was observed after 50-60 min. The effect lasted 90 min.

The experiments on rabbits showed that picamilon (10 mg/kg), injected intravenously into conscious animals, increased the blood flow in the parietal cortex on average by 31 ± 9.1% (Table 1). The effect of picamilon developed immediately after injection of the compound, reached a peak value after 40 min, and continued for 90 min.

The state of the pial arterioles was then studied under the influence of picamilon. Experiments showed that picamilon (0.2 ml of 5% solution), if applied locally, induced dilatation of the pial arterioles after 2-3 sec (Fig. 1). Dilatation was most marked in arterioles with an initial diameter of 10-20 μ (on average by 51 ± 5.2%). With an increase in the diameter of the pial arterioles, the vasodilator effect of picamilon became weaker, and it was weakest of all in arterioles with a diameter of 41-50 μ (on average by 21 ± 4%; $p < 0.001$; Fig. 2).

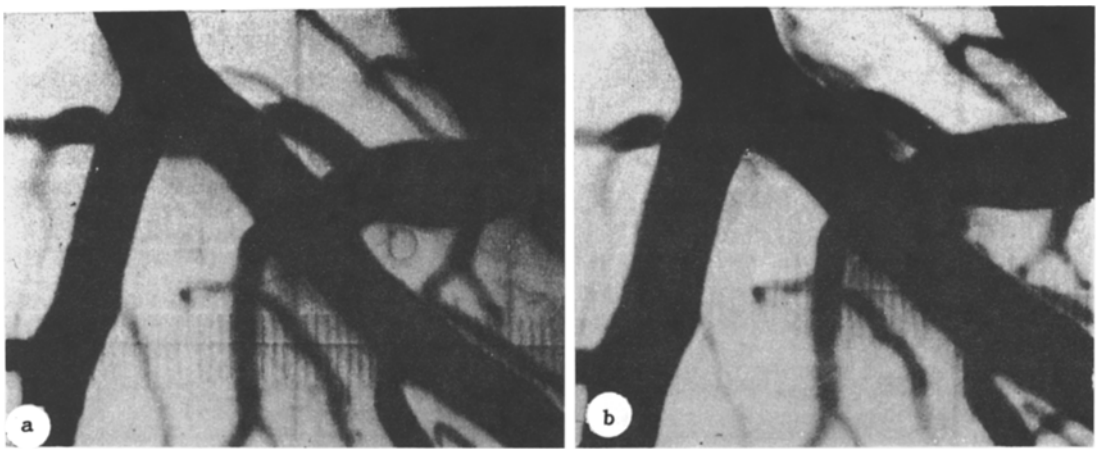

Fig. 2. Photomicrographs of arterioles before (a) and after (b) application of picamilon (0.2 ml of 5% solution).

In these experiments picamilon caused no significant change in the blood pressure. An increase in diameter of the pial arterioles also was observed in experiments with intravenous injection of picamilon in a dose of 20-50 mg/kg.

These results showing more marked dilatation of the pial arterioles with a smaller diameter, under the influence of picamilon, are in agreement with the pattern observed previously, when similar reactions of the pial arterioles to various factors were obtained. Similar changes in the diameter of these vessels were observed in response to lowering of the perfusion pressure [2] and to stimulation of cerebral cortical activity by strychnine [1]. Consequently, the unequal dilatation of pial arteries of different diameter under the influence of picamilon is characteristic response of these blood vessels. The effect of picamilon cannot therefore be linked with unequal sensitivity of pial arterioles of different diameter to the drug. The absence of any change in blood pressure under these circumstances suggests that the vasodilator effect of picamilon is due to the direct influence of the drug on pial arterioles.

Picamilon thus increases the blood supply of the cerebral cortex in conscious rats and rabbits when administered in various ways. Under the influence of the drug dilatation of the pial arterioles is observed as it is but to a more marked degree in vessels with smaller diameter (10-20 μ). The vasodilator effect of the drug is connected with its direct influence on pial arterioles.

LITERATURE CITED

1. D. G. Baramidze, Yu. I. Levkovich, and G. I. Mchedlishvili, Fiziol. Zh. SSSR, 69, No. 8, 1058 (1983).
2. I. V. Gannushkina, The Collateral Circulation in the Brain [in Russian], Moscow (1973).
3. K. Aukland, Acta Neurol. Scand., Suppl. 14, 42 (1965).