CEREBROCRAST AS A CORRECTOR OF POSTISCHEMIC PHENOMENA IN ACUTE TRANSIENT CEREBRAL ISCHEMIA

T. G. Bazhenova, M. B. Plotnikov, T. M. Plotnikova, and A. S. Saratikov

UDC 616.831-005.4-036.11-085.34:546.41].015.23

KEY WORDS: cerebral ischemia; postischemic phenomena; cerebrocrast.

Calcium antagonists of the 1,4-dihydropyridine group are very promising anti-ischemic agents [10]. The cerebroprotective action of these drugs is due to their ability to dilate the cerebral vessels and to improve the cerebral blood flow, to protect neurons against excessive calcium inflow and to prevent triggering of the "ischemic cascade," and to reduce neurotransmitter release [8, 9, 15]. Cerebrocrast [2,6-dimethyl-3,5-bis-(2-propoxyethoxy-carbonyl)-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine] induces selective dilatation of cerebral vessels and prevents exhaustion of the ATP reserves in brain tissue in acute cerebral ischemia [1, 7].

The aim of this investigation was to study the efficacy of cerebrocrast as a corrector of disturbances of the cerebral hemodynamics and of oxygen metabolism of the brain in acute transient ischemia.

EXPERIMENTAL METHOD

Experiments were carried out on 14 male and female cats weighing 2.5-3.5 kg, anesthetized with urethane and chloralose (800 mg/kg and 80 mg/kg respectively), and 15 noninbred rats weighing 250-300 g, anesthetized with urethane (1 g/kg). Cerebral ischemia for 30 min was induced in cats by simultaneous compression of both carotid arteries after preliminary occlusion of the vertebral arteries [5]. The following parameters were evaluated in these experiments: systemic arterial blood pressure (SBP), total cerebral blood flow (TCBF), based on the blood flow into the brain via both internal maxillary arteries (by means of MFV-2100 and MFV-1100 flowmeters), pO_2 in the parietal cortex by a polarographic method, pO_2, pCO_2, and pH of cerebral arterial and venous blood on an ABL-4 gas analyzer. The cats were perfused intravenously with cerebrocrast in a dose of 1 $\mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$ for 1 h, starting immediately after the end of occlusion of the carotid arteries. The effect of cerebrocrast on the affinity of hemoglobin for oxygen was estimated in rats by the method suggested previously [4], with calculation of P_{50} [2]. The compound was injected intravenously into rats for 15 min in a dose of 0.4 $\mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$ 60 min before blood sampling. The results were subjected to statistical analysis by Student's t test and Wilcoxon's nonparametric test [3].

EXPERIMENTAL RESULTS

Occlusion of the carotid arteries in animals of the control group was accompanied by acute hypoxia of brain tissue: pO_2 in the cats' cerebral cortex fell toward the end of ischemia by 56%, and after the end of occlusion, values of pO_2 did not exceed 60% of the initial level throughout the period of observation (Table 1). TCBF after resump-

Department of Pharmacology, Tomsk Medical Institute. Laboratory of Pharmacology of the Circulation, Research Institute of Pharmacology, Tomsk Scientific Center, Russian Academy of Medical Sciences. (Presented by Academician of the Russian Academy of Medical Sciences E. D. Gol'dberg.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 10, pp. 378-380, October, 1992. Original article submitted March 25, 1992.

TABLE 1. Effect of Cerebrocrast on Total Cerebral Blood Flow (TCBF, ml/min), Systemic Blood Pressure (SBP, mm Hg), pO_2 of the Parietal Cortex (mpO_2, percent of initial level), pO_2 in Venous Blood (vpO_2, mm Hg), and pO_2 in Arterial Blood (apO_2, mm Hg), and Brain Oxygen Consumption (CO_2, mg·100 g^{-1}·min^{-1}) in Cerebral Ischemia and Recirculation (mean of seven experiments)

	Parameter	Initial data	Ischemia for 30 min	Recirculation, min				
				1	30	60	90	120
Control	TCBF	17,1±0,8	—	14,7±1,3	11,1±0,9*	9,5±0,9*	8,0±1,2*	8,2±0,8*
	SBP	147±4	162±5*	121±6*	132±6*	124±8*	118±6*	108±6*
	mpO_2	100	44±6*	68±17	60±10*	60±10*	54±11*	47±11*
	vpO_2	41,4±3,3	29,0±3,6*	—	33,9±3,2	26,4±3,5*	28,3±3,3*	23,6±4,7*
	apO_2	96,8±5,0	91,7±5,5	—	95,5±5,1	96,3±4,6	95,9±4,0	96,6±4,2
	CO_2	4,8±0,5	—	—	3,9±0,5	4,7±0,5	4,7±0,3	4,7±0,4
Cerebrocrast	TCBF	20,9±2,4	—	17,3±1,9	18,9±2,2**	19,3±3,7**	19,5±3,0**	17,4±3,0**
	SBP	153±8	195±13*	140±12	144±15	127±8	156±13**	156±14**
	mpO_2	100	28±7*	81±26	87±13**	98±10**	89±8**	82±9**
	vpO_2	41,1±2,9	27,1±3,4*	—	38,3±4,1	42,7±5,1**	39,8±5,4**	37,3±5,4**
	apO_2	107,8±5,0	103,0±11,0	—	108,2±8,6	112,8±9,1	107,4±9,5	105,5±9,8
	CO_2	4,5±0,7	—	—	3,2±0,8	2,1±0,2*,**	3,4±0,8	3,1±0,8

Legend. *$p < 0.05$ compared with initial background, **$p < 0.05$ compared with control.

tion of the blood flow was not restored but remained depressed by 14-53% throughout the period of recirculation. SBP in the postischemic period fell, to reach 73% of the initial value toward the end of observation. The fall of pO_2 of the venous blood (from 41.4 mm Hg to 29.0 mm Hg toward the end of ischemia and to 23.6 mm Hg after 2 h of recirculation) is evidence of episodes of cerebral hypoxia, reaching the critical level [6]. Thus the model of acute transient cerebral ischemia used enables postischemic phenomena of hypoperfusion and hypo-oxygenation of brain tissue to be clearly reproduced.

No significant differences in the values of the parameters studied or in their time course could be found in animals of the control and experimental series before ischemia, at the moment it ended, and after 1 min of recirculation (Table 1).

Infusion of cerebrocrast significantly improved the blood supply to the brain tissue. Despite a moderate fall of SBP, toward the end of infusion of the compound TCBF was close to its initial value, reflecting active reduction by cerebrocrast of the cerebral vascular resistance. In animals of the experimental series TCBF was significantly higher than its value in the control group from the 30th until the 120th minute of recirculation.

Like other selective vasodilators of the 1,4-dihydropyridine group – nimodipine and nicardipine [11, 12], cerebrocrast thus prevents the development of the postischemic hypoperfusion phenomenon. However, despite the favorable character of this effect, improvement of the blood flow by calcium antagonists in the postischemic period does not always correlate with alleviation of the neurologic deficit [13]. These findings led us to study the effect of cerebrocrast on brain oxygen metabolism.

In experiments with infusion of cerebrocrast, starting from 60 min of recirculation and until the end of observation values of pO_2 in the cerebral cortex and of the cerebral venous blood were significantly higher than those in the control group, and in some cases reached the initial values (Table 1). The pO_2 level in cerebral venous blood was above the range of critical values. The antihypoxic action of cerebrocrast, manifested as prevention of lowering of the ATP reserves in brain tissue [1], may have been due not only to limitation of postischemic hypoperfusion, but also to reduction of the oxygen consumption of the brain. A tendency in this direction was exhibited as early as at the 30th minute of infusion of cerebrocrast and toward the end of infusion it became quite well marked (Table 1). The mechanism of reduction of oxygen utilization by the cat brain, caused by this compound, is not sufficiently clear. This effect is evidently due to the depressant effect of the drug on the CNS: it has been shown that cerebrocrast in a dose of 1 μg/kg depressed the basic EEG rhythms in cats only very slightly [1], and in our own experiments the total dose of the drug was significantly higher than that just mentioned, namely 60 μg/kg. Lowering of the oxygen demand of the brain by cerebrocrast makes its own contribution to the mechanisms of the cerebroprotective action of the compound, and a similar effect lies at the basis of the anti-ischemic and antihypoxic activity of barbiturates and sodium hydroxybutyrate [14]. Incidentally, the depressant effect of cerebrocrast on oxygen utilization by the brain is

evidently selective in character and does not extend to brain-stem structures, for the respiration rate and pO_2 of the arterial blood did not change significantly in the course of the experiment (Table 1).

Another mechanism of the alleviation of circulatory cerebral hypoxia by cerebrocrast is reduction of the affinity of hemoglobin for oxygen by the compound. Our experiments on rats showed that intravenous infusion of cerebrocrast led to a marked rise of P_{50} of the blood from 28.0 ± 0.4 mm Hg to 32.0 ± 0.5 mm Hg 1 h after injection of the drug. In animals of the control group this parameter was virtually unchanged (the corresponding values were 28.7 ± 0.4 mm Hg and 28.3 ± 0.4 mm Hg).

Cerebrocrast thus has a beneficial effect on the blood and oxygen supply of the brain in the postischemic period in cats. Intravenous infusion of the preparation after acute ischemia prevents the development of the phenomenon of postischemic hypoperfusion and hypo-oxygenation of brain tissue. The antihypoxic action of cerebrocrast is evidently due to improvement of the cerebral blood supply, reduction of the oxygen consumption by the brain, and lowering of the affinity of hemoglobin for oxygen.

REFERENCES

1. Ya. L. Briede, D. V. Meirena, A. U. Dzena, et al., Synthesis, Pharmacology, and Clinical Aspects of New Psychotropic and Cardiovascular Agents [in Russian], Volgograd (1989), p. 77.
2. I. A. Vinogradova, S. Yu. Bagryantseva, and G. V. Derviz, Probl. Gematol., No. 6, 26 (1981).
3. E. V. Gubler and A. A. Genkin, The Use of Nonparametric Statistical Criteria in Medico-Biological Research [in Russian], Leningrad (1973).
4. M. B. Plotnikov, B. I. Laptev, and T. M. Plotnikova, Farmakol. Toksikol., No. 6, 83 (1989).
5. M. B. Plotnikov and Z. V. Kulakova, Current Problems in Pharmacology and the Search for New Therapeutic Preparations [in Russian], Vol. 4, Tomsk (1990), pp. 194-196.
6. G. A. Ryabov, Hypoxia of Critical States [in Russian], Moscow (1983).
7. G. J. Dubur, M. M. Veveris, G. Weinheimer, et al., Arzneimittel-Forsch., **39**, No. 10, 1185 (1989).
8. K. Hass, Neurol. Clin., **1**, 345 (1983).
9. K.-A. Hossmann, W. Paschen, and Z. Csiba, J. Cereb. Blood Flow Metab., **3**, 346 (1983).
10. G. Johnson and F. W. Marcoux, Ann. Rep. Med. Chem., **21**, 109 (1986).
11. L. N. Milde, J. H. Milde, and J. D. Michenfelder, J. Cereb. Blood Flow Metab., **6**, 332 (1986).
12. T. Sakabe, I. Nagai, T. Ishikawa, et al., J. Cereb. Blood Flow Metab., **6**, 684 (1986).
13. T. Sakabe, Magnesium, **8**, 232 (1989).
14. M. Smialek, I. Klatzko, and M. Spatz, Cerebral Vascular Disease, Amsterdam (1979), pp. 186-192.
15. V. Voiculescu, Rev. Roum. Med., **27**, No. 3, 175 (1989).