LITERATURE CITED

1. C. D. Blaha and R. F. Lane, Neurosci. Lett., **78**, 199 (1987).
2. M. W. Goosey and N. S. Doggett, Biochem. Pharmacol., **32**, 2411 (1983).
3. R. R. Guinetdinov, M. B. Bogdanov, V. M. Pogorelov, et al., Neuropharmacology, **30**, No. 11, 1251 (1991).
4. J. R. Hollerman and A. A. Grace, Neurosci. Lett., **96**, 82 (1989).
5. J. Ichikawa and H. Y. Meltzer, Brain Res., **507**, 138 (1990).
6. A. Imperato, A. Mulas, and G. Di Chiara, Eur. J. Pharmacol., **142**, 177 (1987).
7. J. C. Miller and A. J. Friedhoff, Biochem. Pharmacol., **28**, 688 (1979).
8. S. O. Ogren and T. Hogberg, ISI Atlas of Science: Pharmacology (1988), pp. 141-147.
9. R. I. Rimon, P. Averbuch, L. Rozick, et al., Psychopharmacology, **73**, 197 (1981).
10. R. H. Roth, Neuroleptics, Neurochemical Behavioral and Clinical Perspectives, ed. by J. T. Coyle and S. J. Enna, New York (1983), pp. 119-157.
11. P. Seeman, Pharmacol. Rev., **32**, 229 (1980).
12. B. H. Westerink and J. B. de Vries, Neurosci. Lett., **99**, 197 (1989).
13. P. Worms, C. L. E. Broekkamp and K. G. Lloyd, Neuroleptics: Neurochemical, Behavioral and Clinical Perspectives, ed. by J.T. Coyle and S.J. Enna, New York (1983), pp. 93-119.
14. S. Yamada, H. Yokoo, S. Harajiri, et al., Eur. J. Pharmacol., **192**, 141 (1991).
15. T. Zetterstrom, T. Sharp, and U. Ungerstedt, Naunyn-Schmiedeberg's Arch. Pharmakol., **334**, 117 (1986).

EFFECT OF CEREBROCRAST ON LOCAL CEREBRAL BLOOD FLOW AND EEG IN CATS AFTER BRAIN HEMORRHAGE

G. A. Chernysheva, M. B. Plotnikov, É. A. Bisenieks, N. V. Makarova, Ya. R. Uldriks, and G. Ya. Dubur

UDC 616.831-031.81-003.215.092.9-085.31:546.41/.015.23-036.8-07

KEY WORDS: brain hemorrhage; calcium antagonists; cerebral blood flow; EEG

The high efficacy of 1,4-dihydropyridine derivatives in the treatment of acute cerebrovascular disturbances [7, 13] justifies a further search for correctors of the cerebral hemodynamics among this group of compounds. A new preparation, cerebrocrast has been synthesized at the Institute of Organic Synthesis, Academy of Sciences of Latvia, and has a marked selective action on the cerebral vessels and significantly increases the volume velocity of the total cerebral blood flow in anesthetized animals [5].

The aim of this investigation was to study the effect of cerebrocrast on the local cerebral blood flow of conscious animals, under normal conditions and with chronic vasospasm after intracerebral hemorrhage, and to compare it with the effect of the most active cerebral vasodilator of the 1,4-dihydropyridine group, namely nimodipine, and also to evaluate the effect of cerebrocrast on the EEG in this pathology.

Laboratory of Pharmacology of the Cerebral Circulation, Research Institute of Pharmacology, Tomsk Scientific Center, Academy of Medical Sciences of Russia. Institute of Organic Synthesis, Academy of Sciences of Latvia, Riga. (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. 7, pp 49-52, July, 1992. Original article submitted November 27, 1991.

 0007-4888/92/0007-0974$12.50

TABLE 1. Effect of 60-min Intravenous Infusion of Cerebrocrast and Nimodipine in a Dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on Local Cerebral Blood Flow of Conscious Cats (in $ml \cdot 100\ g^{-1} \cdot min^{-1}$)

Preparation	Structure	Background	Change relative to background, h					
			0.5	1	1.5	2	2.5	3
Cerebrocrast	Visual cortex	55,7±9,8	0,3±1,2	1,5±1,5	5,8±2,1*	5,1±2,9	6,1±2,8	8,0±2,4*
	Thalamus	56,1±5,1	4,6±2,2	4,6±1,6*	4,6±1,7*	5,5±2,1*	5,1±3,4	6,6±4,2
	Reticular formation	49,7±3,0	0,6±1,5	2,6±1,8	1,9±0,9	3,6±2,3	6,7±2,7*	9,0±6,1
Nimodipine	Visual cortex	56,7±12,4	5,2±2,3*	6,9±2,9*	4,9±2,4	4,3±4,2	2,9±4,2	8,5±5,1
	Thalamus	55,5±7,4	2,9±5,7	6,6±2,3*	8,1±3,7	9,1±2,2*	−0,7±2,6	1,0±3,0
	Reticular formation	52,9±3,7	6,0±3,1	6,6±2,4*	6,4±2,6*	0,5±3,4	−0,4±3,8	−0,5±3,5

Legend: here and in Table 2, *p < 0.05.

TABLE 2. Effect of 60-min Intravenous Infusion of Cerebrocrast and Nimodipine in a Dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on Local Cerebral Blood Flow of Conscious Cats 1-2 Days after Hemorrhage (in $ml \cdot 100\ g^{-1} \cdot min^{-1}$)

Preparation	Structure	Initial background	Pathological background	Change relative to pathological background, H					
				0.5	1	1.5	2	2.5	3
Cerebrocrast	Left hemisphere								
	Visual cortex	51,7±4,1	42,3±5,2	1,9±1,1	7,2±1,6*	3,7±1,1*	3,7±1,3*	1,0±1,9	5,6±2,5*
	Thalamus	59,0±3,0	50,7±5,6	5,3±1,9*	8,9±4,1*	6,0±2,7*	2,3±2,9	8,4±4,8	8,2±5,6
	Reticular formation	56,0±3,4	49,8±4,5	5,0±1,6*	6,6±5,4	10,0±4,5*	3,7±3,3	4,4±1,6*	6,2±4,3
	Right hemisphere								
	Visual cortex	51,0±2,6	43,8±3,7	10,3±3,3*	6,1±3,4*	7,5±2,1*	9,5±2,3*	12,3±1,9*	9,9±2,9*
	Thalamus	66,4±4,5	54,1±4,0	4,0±3,1	9,8±3,2*	6,9±3,0*	2,3±3,0	4,8±3,3	−0,8±2,6
	Reticular formation	55,4±3,1	45,8±2,5	4,5±1,9*	7,6±2,1*	11,6±3,9*	7,2±2,1*	3,0±2,1	6,2±1,4*
Nimodipine	Left hemisphere								
	Visual cortex	58,3±11,0	48,5±7,6	0,5±1,3	7,6±1,5*	5,9±2,2*	5,6±2,9	9,0±3,7*	10,9±3,4*
	Thalamus	58,4±4,0	45,2±8,2	5,8±2,3*	5,3±1,9	3,1±1,4	7,7±2,5*	7,4±3,4	5,2±2,5
	Reticular formation	49,6±2,7	39,5±4,1	1,1±1,8	11,0±3,4*	7,9±2,6*	11,1±2,9*	5,2±2,4	4,5±2,9
	Right hemisphere								
	Visual cortex	46,0±2,3	37,1±4,2	5,1±2,4	3,8±1,0*	4,6±0,9*	3,2±1,2	2,2±1,4	−0,7±1,3
	Thalamus	61,2±3,6	50,0±3,3	5,1±1,7	10,2±2,8*	4,4±1,0*	4,0±0,7*	3,2±1,3	0,6±0,8
	Reticular formation	56,9±3,0	42,7±3,7	5,6±5,8	8,8±3,9*	7,1±2,1*	7,1±4,3	3,8±3,2	2,3±3,4

EXPERIMENTAL METHOD

Experiments were carried out on 17 conscious cats before and 1-2 days after the creation of intracerebral hemorrhage (ICH) by injection of 1.5 ml of autologous blood into the right internal capsule through a previously implanted needle [1]. The local cerebral blood flow (LCBF) in the left and right visual cortex, thalamus, and mesencephalic reticular formation was determined by the hydrogen clearance method [2]. The systemic blood pressure was measured in the right carotid artery. The EEG recorded in the visual cortex and the thalamus of the left and right hemispheres was analyzed by means of a Berg–Fourier analyzer, relative to distribution of the power of the spectrogram for a period of 248 sec in transmission bands 0-16, 0-2, 2-4, 4-8, 8-12, and 12-16 Hz, with time constant of 0.03 sec, and the abundance of individual frequency components was calculated as percentages of the total power of the spectrum for the whole hemisphere. Cerebrocrast and the comparison drug nimodipine (from "Bayer") were injected intravenously in a dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the course of 60 min. The results were subjected to statistical analysis, within series by Student's t test for paired comparisons, and between series by the Wilcoxon–Mann–Whitney test.

EXPERIMENTAL RESULTS

In conscious cats LCBF in the visual cortex, thalamus, and mesencephalic reticular formation averaged 54.0 ± 6.8 ml·100 g^{-1}·min^{-1}. Injection of cerebrocrast into intact animals led to a moderate increase in LCBF in the structures tested, but only after infusion of the drug had ended (Table 1). In response to injection of nimodipine, a similar increase in LCBF developed in the cortex actually during infusion of the drug, but in the thalamus and mesencephalic reticular formation after end of the infusion also.

Reduction of the LCBF on average by 14-25%, more marked on the right side, was observed compared with the initial background 1-2 days after ICH. This was due to the development of a state of chronic cerebral vasospasm [3] and is in agreement with results obtained during the study of the cerebral hemodynamics in patients with intracerebral hemorrhage [8].

Intravenous injection of cerebrocrast into cats with ICH led to a significant rise of LCBF, starting with the 30th minute of infusion (Table 2). Injection of nimodipine against the background of ICH also significantly increased LCBF in the thalamus and mesencephalic reticular formation, and increased it moderately in the visual cortex of both hemispheres (Table 2).

Neither cerebrocrast nor nimodipine caused the "intracerebral steal" phenomenon: a marked increase in LCBF was observed both in structures remote from the focus of bleeding and in areas closest to it (thalamus of the right hemisphere). This is in agreement with clinical data obtained by other workers, who observed an increase in blood supply under the influence of 1,4-dihydropyridines in zones close to the ischemic focus after intracerebral or subarachnoid hemorrhage, which was not less, and in some cases was even greater ("steal back" phenomenon) than in the contralateral hemisphere [6, 12].

Comparison of the magnitude of the response to injection of the drugs before and 1-2 days after ICH showed that the increase in LCBF in response to cerebrocrast, given against the background of chronic spasm of the cerebral vessels in the right reticular formation (1-1.5 h of the experiment) and visual cortex (after 30 and 150 min of observation on the right and 60 min on the left) was significantly greater than after injection of the drug into intact animals. In the cerebral vessels, in which an intracellular system of calcium sequestration is inadequately developed, the inflow of this ion plays a leading role in the creation and maintenance of a state of spasm [11]. After ICH, we demonstrated the most intensive spasm in vessels of medium and small caliber [3], in agreement with data showing an increase in the contribution of extracellular calcium to regulation of cerebrovascular tone with a decrease in their diameter [4]. The ability of 1,4-dihydropyridines and, in particular, of cerebrocrast, to block voltage-controlled channels of the plasma membranes of the smooth-muscle cells of the cerebral vessels [5] evidently leads to restriction of the excessive inflow of calcium ions into the myocytes, and ultimately is accompanied by an increase in LCBF; under conditions of spasm, moreover, the response exceeds that observed in intact animals. Meanwhile, infusion of nimodipine caused a response of similar magnitude of LCBF in both cases, except that in the left reticular formation, after 2 h of the experiment, a significantly greater increase was observed in the blood flow in response to injection of the drug after ICH compared with intact cats.

ICH in cats caused considerable disturbances of brain electrical activity: in the absence of any significant changes in the relative power of the θ-band, the power of the δ-waves rose significantly and the power of the α- and β-waves fell. In the thalamus, the power of δ-activity rose by more than 2.5 times, largely on account of waves with a frequency of 0-2 Hz (from 4-5% to 19-24% relative to the total power of the spectrum). Power in the α- and β-bands of activity fell by 1.4-1.6 and 1.9-2.1 times respectively. An increase in power of δ-activity (by 2.2-2.5 times) also was recorded in the cortex of both hemispheres and was accompanied by inhibition of power of the spectra in the α- and β-bands (by 1.4-1.5 and 1.8-2.2 times respectively). Injection of cerebrocrast led to a decrease in power of the spectrum in the slow-wave region and an increase in power in the region of α- and β-activity in all structures studied. The power of the δ-wave region of the spectrum was reduced by 1.2-1.5 times: in the thalamus mainly due to inhibition of activity of frequency up to 2 Hz, in the cortex due to a uniform decrease in power of the spectrum in the region of frequencies of 0-2 and 2-4 Hz. During infusion of cerebrocrast the power of the spectrum of the α- and β-waves was increased in the right thalamus, but 0.5-1 h after injection of the preparation the power of the high-frequency band of the spectrum increased in all the structures studied. An increase in relative power of the theta-waves was observed in the cortex and thalamus of both hemispheres toward the end of infusion of the drug, and also 1 h after injection of the preparation in the right and left cortex (Fig. 1).

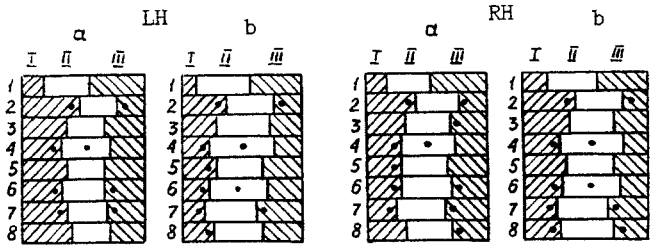

Fig. 1. Effect of intravenous infusion of cerebrocrast in a dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on relative power of δ- (I), θ- (II), and (α + β)-waves (III) in the thalamus (a) and visual cortex (b) of both hemispheres. 1) Initial background, 2) 1 day after hemorrhage, 3-8) relative power 0.5, 1, 1.5, 2, 2.5, and 3 h respectively after beginning of infusion of preparation. Dots indicate significant changes ($p < 0.05$) compared with initial (2) or pathological background (3-8). LH) Left hemisphere, RH) right hemisphere.

According to data in the literature, nimodipine has a similar protective action on brain electrical activity, namely increasing the relative power of the α- and β-waves and decrease in the relative power of the δ-waves, in cerebral ischemia [10]; some workers, moreover, associate the antiischemic action of the drug with a direct effect on neurons [9].

Infusion of cerebrocrast and nimodipine caused no significant changes in the systemic blood pressure of conscious cats.

Injection of cerebrocrast into cats in the stage of chronic cerebral spasm after ICH thus leads to a significant increase in blood flow in the thalamus, mesencephalic reticular formation, and visual cortex without an intracerebral steal syndrome and has a favorable effect on brain electrical activity. Cerebrocrast is not inferior to nimodipine in the effectiveness of its action on the cerebral hemodynamics.

LITERATURE CITED

1. E. N. Lerner and L. I. Bibileishvili, Electrophysiology of the Nervous System [in Russian], Rostov-on-Don (1963), pp. 226-228.
2. M. B. Plotnikov, Fiziol. Zh. SSSR, No. 11, 1734 (1975).
3. M. B. Plotnikov and A. S. Saratikov, Vopr. Neirokhir., No. 5, 33 (1981).
4. K.-E. Andersson, Neurol. Regul. Brain Circ., 67 (1986).
5. G. Ya. Dubur (G. J. Dubur), M. M. Veveris, G. Weirheimer, et al., Arzneimittel. Forsch., **39**, No. 10, 1185 (1989).
6. H. J. Gelmers, Acta Neurochir. (Vienna), **63**, 283 (1982).
7. H. J. Gelmers, K. Gorter, C. J. Weerdt, et al., New Engl. J. Med., **313**, No. 4, 203 (1988).
8. H. Kawakami, T. Katsusava, K. Uemura, et al., Stroke, **5**, 207 (1974).
9. V. Kraaier, A. C. van Huffelen, and G. H. Wieneke, Eur. J. Clin. Pharmacol., **40**, No. 1, 17 (1991).
10. H. Mabe, H. Nagai, T. Takagi, et al., Stroke, **17**, No. 3, 501 (1986).
11. J. Marin, Gen. Pharmacol., **3**, 295 (1988).
12. B. L. Philippon, L. Chacornac, M. Monterry, et al., Eur. J. Nucl. Med., **15**, No. 8, 409 (1989).
13. J. Philippon, R. Grob, and F. Dagreou, Acta Neurochir. (Vienna), **82**, 110 (1986).