2. N. V. Kaverina, Z. P. Senova, and V. V. Lyskovtsev, Kardiologiya, No. 4, 67 (1978).
3. V. V. Lyskovtsev, Z. P. Senova, I. A. Yuryavichyus, et. al., Byull. Éksp. Biol. Med., No. 3, 243 (1979).
4. L. V. Rozenshtraukh, R. L. Ver'e, and B. Lown, Vestn. Akad. Med. Nauk SSSR, No. 10, 52 (1978).
5. L. V. Rozenshtraukh, R. Raffi, V. Elkharar, et al., Kardiologiya, No. 5, 63 (1979).
6. L. V. Rozenshtraukh, V. A. Saks, I. A. Yuryavichyus, et al., Fiziol. Zh. SSSR, No. 3, 405 (1979).
7. Z. P. Senova and V. V. Lyskovtsev, Farmakol. Toksikol., No. 3, 293 (1976).
8. I. A. Yuryavichyus, V. V. Rozenshtraukh, A. I. Undrovinas, et al., Kardiologiya, No. 9, 118 (1978).
9. P. Danilo, W. B. Langan, M. R. Rosen, et al., Eur. J. Pharmacol., 45, 127 (1977).

EFFECT OF DIAZEPAM AND PHENAZEPAM ON NERVOUS REGULATION OF THE CEREBRAL CIRCULATION

R. S. Mirzoyan, T. S. Gan'shina, I. V. Kosarev, and É. A. Bendikov

UDC 615.214.22:547.891.2].014.4:612.824

KEY WORDS: diazepam; phenazepam; cerebral circulation; cerebrovascular reflexes.

According to data in the literature, diazepam reduces the cerebral blood flow [11-13]. Chai and Wang [10] found that diazepam inhibits pressor responses of the arterial blood pressure (BP) to stimulation of the carotid sinus, medulla, and hypothalamus. It also has an antihypertensive effect during emotional stress [4]. However, reports have been published that diazepam may increase the intensity of pressor vasomotor reflexes in animals under general anesthesia and in unanesthetized, curarized cats [3, 8, 9]. As regards phenazepam, there is no information in the literature on its effect on the cerebral hemodynamics.

The object of the present investigation was to study the effect of diazepam and phenazepam on nervous regulation of the cerebral blood supply.

EXPERIMENTAL METHOD

Experiments were carried out on 63 cats under general anesthesia (urethane and chloralose) with artificial ventilation of the lungs and on seven waking cats.

The cerebral blood flow was determined by the ^{133}Xe method on the VAV-100 apparatus. The results were subjected to statistical analysis on the Minsk-22 computer. The value of the blood flow was determined by successive derivation of exponential functions [6]. The state of the cerebral circulation also was judged from the inflow of blood into the cat's brain through the internal maxillary artery, which was recorded by means of an electromagnetic measuring device in acute and chronic experiments. The EEG was recorded in the parietal region, the ECG in lead II, and BP in the femoral artery. The vascular component of the action of the drugs on the cerebral hemodynamics was differentiated by separate perfusion of the carotid and vertebral arteries on the two sides [5]. The acid–base balance and partial pressure of oxygen was determined in samples of arterial blood and CSF by the ABC-1 apparatus. Tonic and reflex activity were recorded in the sympathetic nerves with differentiation of responses to impulses from afferent fibers of groups A and C, and postactivation inhibition and inhibition of somatosympathetic responses evoked by excitation of low-threshold spinal afferents also were estimated [1]. Diazepam and phenazepam were injected intravenously in doses of 0.05 and 0.5 mg/kg.

Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 9, pp. 305-308, September, 1980. Original article submitted November 16, 1979.

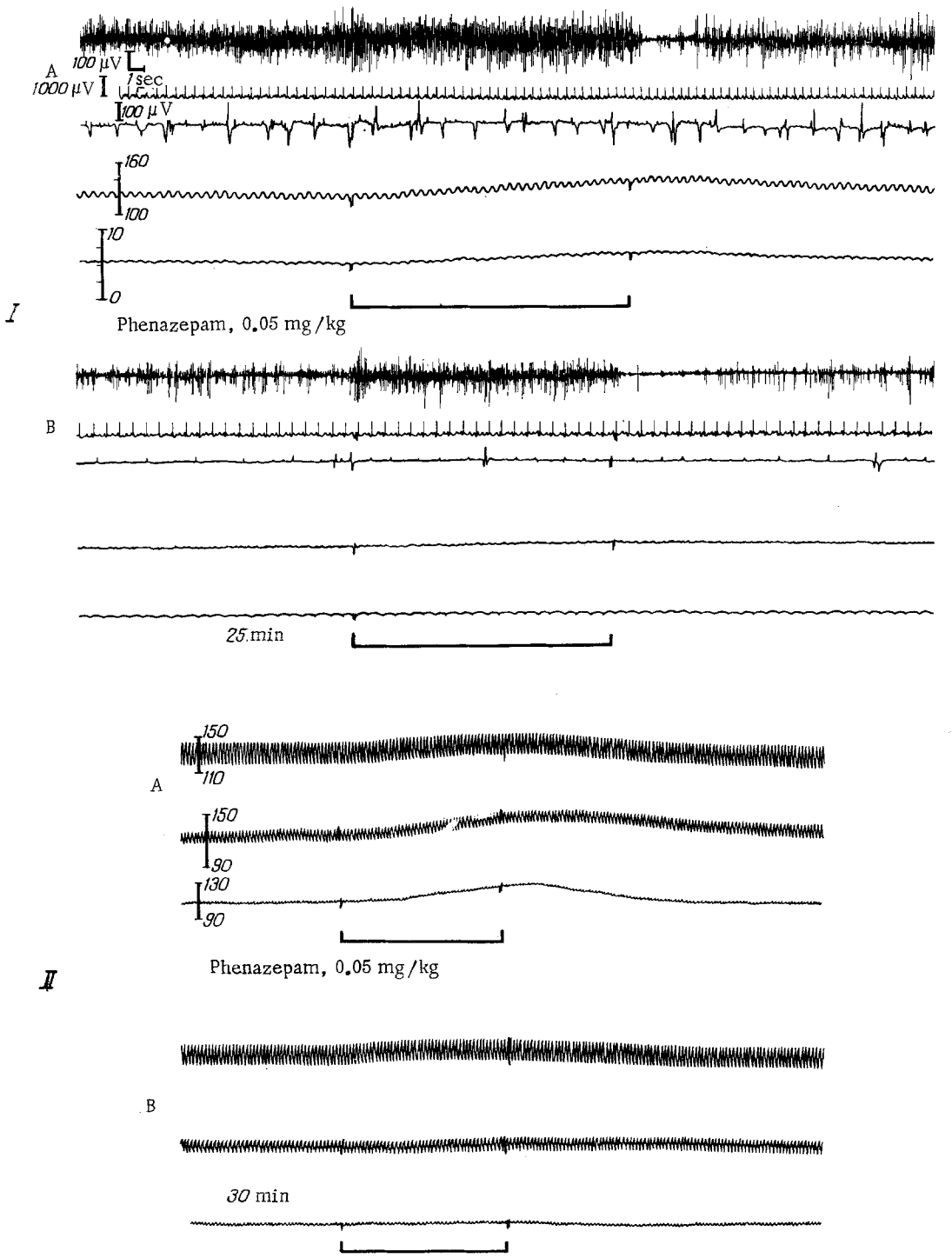

Fig. 1. Effect of phenazepam (0.05 mg/kg, intravenously) on changes in cerebral blood flow (I) and on tone of cerebral vessels (II) evoked by electrical stimulation of afferent fibers of tibial nerve. I: A) Control response, B) 25 min after injection of phenazepam. From top to bottom: tonic and reflex activity in renal sympathetic nerve, ECG in lead II, EEG from parietal region, BP in femoral artery, blood flow in internal maxillary artery; stimulation indicated by horizontal line (20 V, 8 stimuli/sec, 1 msec); II: A) control response, B) 30 min after injection of phenazepam. From top to bottom: perfusion pressure in carotid basin, in vertebrobasilar system, BP (in mm Hg), stimulation indicated by horizontal line (20 V, 20 stimuli/sec, 1 msec).

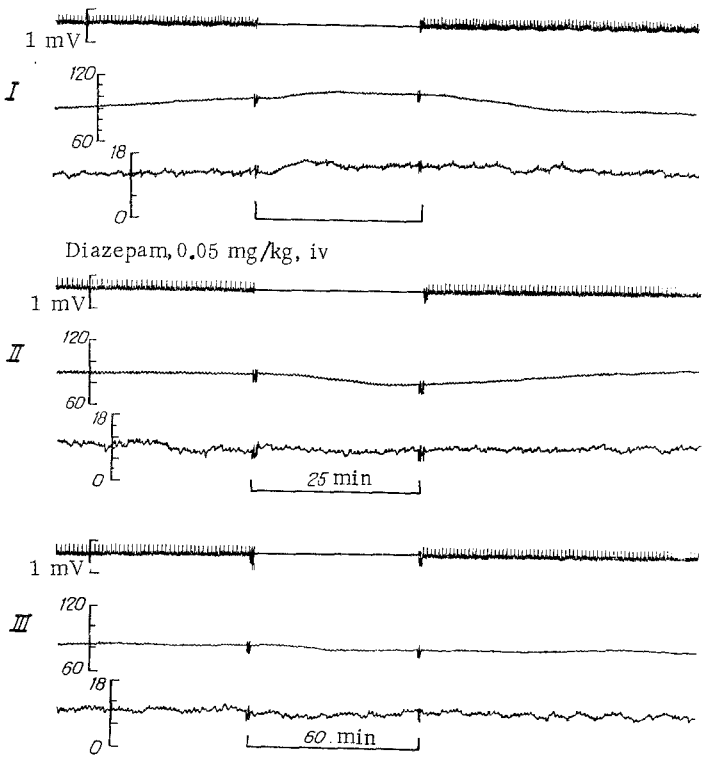

Fig. 2. Effect of diazepam (0.05 mg/kg, intravenously) on changes in cerebral circulation and BP in waking cat evoked by electrical stimulation of spine by subcutaneous bipolar electrodes. I) Control response, II, III) 35 and 60 min after injection of diazepam. From top to bottom: ECG in lead II, BP in femoral artery (in mm Hg), blood flow in internal maxillary artery (in ml/min), stimulation indicated by horizontal line (8 V, 16 stimuli/sec, 2 msec).

EXPERIMENTAL RESULTS

The experiments on cats under general anesthesia showed that diazepam, in doses of 0.05 and 0.5 mg/kg, reduced the blood supply to the brain by 33 ± 5.6 and 39 ± 4.7%, respectively. The BP level was lowered by 43 ± 5.6 and 42 ± 4.2%. Phenazepam in a dose of 0.05 mg/kg reduced the cerebral blood flow (by 20 ± 4.8%; $P < 0.02$) and lowered BP (by 14 ± 3.3%; $P < 0.002$) by a lesser degree than diazepam (Fig. 1).

In experiments by the method of separate perfusion of the carotid and vertebrobasilar arteries on the two sides, the ability of the drugs to lower cerebrovascular tone was revealed. Diazepam (0.05 mg/kg) reduced the resistance of the vessels in the carotid (11 ± 2.6%) and vertebrobasilar (11 ± 2.8%) basins, Phenazepam (0.05 mg/kg) lowered vascular tone in these arterial systems of the brain by 9 ± 1.4 and 9.5 ± 2%, respectively. The cerebrovascular and hypotensive effects of diazepam and phenazepam developed against a background of inhibition of tonic activity in the sympathetic nerves (Fig. 1).

Diazepam and phenazepam inhibited EEG discharges evoked by chloralose (50 mg/kg). A considerable decrease in the amplitude and frequency of these discharges was observed when phenazepam was given in doses of 0.05 and 0.5 mg/kg and diazepam in a dose of 0.5 mg/kg. In the doses tested they had no significant effect on the ECG.

Diazepam, in a dose of 0.05 mg/kg, under conditions of stabilized respiration, did not change pH, pCO_2, or pO_2 in the CSF 3 and 30 min after injection.

In waking cats diazepam, in doses of 0.05 and 0.5 mg/kg, caused no significant changes in the cerebral blood flow. In some experiments, however, a very small decrease in the cerebral blood flow was observed. In most experiments diazepam (0.05 and 0.5 mg/kg) caused a small decrease in BP (Fig. 2).

The study of the effect of diazepam and phenazepam on nervous regulation of the cerebral circulation began with an investigation of their action on the cerebral blood flow during the formation of vasomotor pressor reflexes. Diazepam in a dose of 0.5 mg/kg, considerably inhibited changes in the cerebral circulation during the reflex on average by 80 ± 10.6%. Pressor reflex responses of BP were inhibited (86 ± 5.0%) at the same time. Phenazepam, in a dose of 0.05 mg/kg, had a marked depriming effect on the changes in the cerebral blood supply (70 ± 11%) and on the pressor responses of BP (40 ± 8.5%; see Fig. 1). Diazepam and phenazepam weakened the constrictor reflexes of the cerebral vessels in the systems of the carotid and vertebral arteries, and also the pressor responses of BP. The inhibitory effect of the drugs developed in the course of 5-30 min and continued throughout the experiment (90-120 min or more).

A characteristic feature of the action of diazepam and phenazepam (0.05 and 0.5 mg/kg) was potentiation of central inhibition of tonic and reflex activity in the sympathetic nerves, the factor responsible for the inhibition of cerebrovascular reflexes by these drugs (Fig. 1). In particular, the inhibitory component from afferent low-threshold fibers of somatic nerves and also the process of postactivation inhibition were potentiated. Transformation of somatosympathetic reflex responses from high-threshold afferent fibers was observed.

Reflex changes in the cerebral blood flow and BP under the influence of diazepam also were studied in waking animals. For this purpose electrical stimulation was applied in the region of the spine by subcutaneous bipolar electrodes (2-10 V, 8-16 stimuli/sec, 2 msec). The experiments showed that diazepam (0.05 and 0.5 mg/kg) in most cases weakened the changes in the cerebral blood flow in the period of formation of the vasomotor reflex. The reflex hypertensive response of BP also was inhibited (Fig. 2).

These experiments thus demonstrated that diazepam and, to a lesser degree, phenazepam reduce the blood supply to the brain in animals under general anesthesia, evidently as a consequence of the development of hypotension by the animals. Meanwhile the drugs have a depriming effect on changes in the cerebral flood flow and on the tone of the cerebral vessels, caused by stimulation of afferent fibers of the vagus nerve. They stimulate processes of central inhibition of tonic and reflex activity in the sympathetic nerves and also reduce the amplitude and frequency of potentials on the EEG. The depriming action of phenazepam on nervous regulation of the cerebral circulation, incidentally, is stronger than that of diazepam. The effects of diazepam and phenazepam are similar to the action of GABA [2], which suggests that a GABA-ergic mechanism participates in the action of these drugs not only at the cortical neuronal level [7, 14], but also in central systems of regulation of the cerebral circulation and BP.

LITERATURE CITED

1. É. A. Bendikov and V. G. Butuzov, in: Pharmacology of Monoaminergic Processes [in Russian], Moscow (1971), p. 24.
2. É. A. Bendikov, L. M. Shmuilovich, and V. M. Kopelevich, Byull. Éksp. Biol. Med., No. 1, 65 (1972).
3. N. V. Kaverina, Yu. B. Rozonov, and G. G. Chichkanov, in: Pharmacology and Toxicology [in Russian], No. 9, Kiev (1974), p. 119.
4. M. M. Kozlovskaya and A. Beshimov, in: A Pharmacological Study of Hypotensive Drugs with Central Action, edited by A. V. Val'dman [in Russian], Leningrad (1975), p. 16.
5. R. S. Mirzoyan, Fiziol. Zh. SSSR, No. 6, 966 (1973).
6. R. S. Mirzoyan, A. V. Runov, Yu. M. Varentsov, et al., Byull. Éksp. Biol. Med., No. 2, 48 (1975).
7. R. U. Ostrovskaya, G. M. Molodavkin, R. P. Porfir'eva, et al., Byull. Éksp. Biol. Med., No. 3, 50 (1975).
8. Yu. B. Rozonov, Farmakol. Toksikol., No. 2, 163 (1976).
9. Yu. B. Rozonov, G. G. Chichkanov, and V. A. Raiskii, Farmakol. Toksikol., No. 2, 225 (1973).
10. C. Y. Chai and S. C. Wang, J. Pharmacol. Exp. Ther., 154, 271 (1966).
11. A. Cotev and M. N. Shalit, Anesthesiology, 43, 117 (1975).

12. T. Maekawa, T. Sakaba, and H. Takeshita, Anesthesiology, 41, 398 (1974).
13. E. Pasztor, S. Toth, and G. Benoist, in: The Blood Supply of the Brain [in Russian], Tbilisi (1974), p. 24.
14. V. V. Zakusov, R. U. Ostrovskaya, V. V. Markovitch, et al., Arch. Int. Pharmacodyn., 214, 188 (1975).

EFFECT OF NONACHLAZINE ON THE CARDIAC COMPONENT OF THE BARORECEPTOR REFLEX IN UNANESTHETIZED CATS

O. S. Medvedev, N. A. Stepochkina, and D. D. Matsievskii

UDC 615.224:547.869.2].015.4:612.178.6

KEY WORDS: nonachlazine; pressor response of arterial pressure; Mayer's waves; baroreceptor reflex.

After intravenous injection of the new Soviet antianginal drug nonachlazine a phase of elevation of the arterial blood pressure (BP) lasting 20-30 min is observed [2]. No conclusions regarding the mechanism of onset of the pressor response can yet be drawn from the results of electrophysiological investigations [1], for we do not know how the function of the baroreceptor reflex changes during this period.

Accordingly the investigation described below was undertaken to study the structure of the pressor response and to analyze changes in the cardiac component of the baroreceptor reflex following injection of nonachlazine into unanesthetized animals.

EXPERIMENTAL METHOD

Eighteen chronic experiments were carried out on 14 male cats. Under pentobarbital anesthesia (40 mg/kg, intraperitoneally), 3-4 days before the experiments and under sterile conditions, aortic and venous polyethylene catheters connected to a miniature cock were inserted into the cats [7]. In some experiments, to record the cardiac output, the probe of an ultrasonic doppler flowmeter designed by one of the authors [6] or the probe of an electromagnetic flowmeter (MF-6, Nihon Kohden) was placed in the ascending part of the arch of the aorta. To test the baroreceptor reflex, BP was artificially raised by constricting the descending thoracic aorta by means of an implanted silicone occluder [8]. In the course of the experiments BP was measured with an EMT-35 electromanometer (Elema-Schonander), and the momentary cardiac frequency (CF) was recorded periodically by means of a digital cardiotachometer, triggered by the pulse waves of BP. All the hemodynamic parameters studied were recorded in analog form on a Mingograph-81 apparatus and in digital form by means of a SHCH1413 digital voltmeter and CHZ-34A digital frequency meter on a digital printer of the 3512 type (East Germany).

The following drugs were used in the investigation: nonachlazine (Research Institute of Pharmacology, Academy of Medical Sciences of the USSR), propranolol (Obsiden, East Germany); isoproterenol (Euspiran, Czechoslovakia). All the drugs were diluted with sterile physiological saline and injected intravenously.

The results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

Nonachlazine, in a dose of 1 mg/kg, caused a very small increase in BP in some experiments. The mean values of BP changed from 103.0 ± 3.3 mm Hg in the control to 110 ± 3.5 mm Hg ($P > 0.1$) after injection of the drug. CF remained unchanged at 166 beats/min. An increase

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 9, pp. 309-311, September, 1980. Original article submitted January 16, 1980.

