CHANGES IN THE CEREBRAL CIRCULATION PRODUCED BY VASODILATORS

R. S. Mirzoyan and Yu. M. Varentsov

UDC 612.824.014.46:615.225.2

The volume velocity of the cerebral blood flow was recorded in dogs with the aid of radioactive xenon-133. Papaverine and intensain were found to cause a marked increase in the cerebral blood flow. By bilateral separate perfusion of the maxillary and vertebral arteries it was shown that these changes in the intracranial blood flow are due to the direct action of the drugs on the cerebral vessels. Papaverine lowers the tone of the cerebral vessels equally, while intensain has a more marked effect on the maxillary vessels, and gives a much smaller decrease in the resistance of the resistive brain vessels supplied with blood from the vertebral arteries. The results indicate that the intracranial vessels supplying the cerebral hemispheres differ in their sensitivity to intensain from those supplying blood to the medulla and pons.

Papaverine is widely used in neurological practice for the treatment of cerebrovascular diseases. However, the experimental data for its effect on the cerebral circulation are contradictory. According to some investigators papaverine increases the circulation in the brain tissue [4, 7, 9], while others [10, 11], using nitrous oxide and radioactive krypton-85 in their experiments, found no marked changes in the cerebral hemodynamics. According to Saratikov et al. [5] papaverine, if injected intravenously in doses not affecting the systemic arterial pressure, does not produce changes in the cerebral circulation. However, these workers observed a marked increase in the intracranial blood flow in experiments in which papaverine was injected by the intracarotid route.

No experimental data for the effect of the new coronary vasodilator intensain on the intracranial circulation could be found in the literature. Nevertheless, diseases of the blood vessels of the heart and brain are often described as manifestations of the cardiac and cerebral forms of hypertension.

For this reason the investigation described below was carried out to study the effect of papaverine and intensain on the cerebral hemodynamics.

EXPERIMENTAL METHOD

Experiments were carried out on 46 dogs weighing 18-25 kg anesthetized with morphine (10 mg/kg) and urethane (1 g/kg) and on 43 cats weighing 3-4 kg, anesthetized with urethane (0.6 g/kg) and chloralose (50 mg/kg).

In the experiments of series I the cerebral blood flow was determined quantitatively by intracarotid injection of radioactive xenon-133 [2, 6, 8]. Excretion curves were obtained by means of a single-channel "Ksenon" apparatus [3]. This consists of a collimated detector, radiometer, intensimeter, and automatic writer. The height of the collimator was 50 mm and the diameter of the aperture 50 mm. The detector was placed above the parietal region of the dog's brain. Physiological saline was added to the air–xenon mixture, which was then injected into the right common carotid artery from a syringe.

Laboratory of Pharmacology of the Cardiovascular 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. 75, No. 2, pp. 46-48, February, 1973. Original article submitted January 25, 1972.

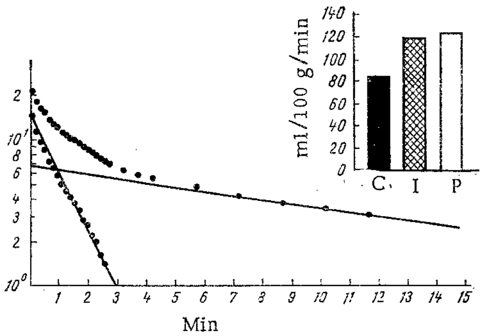

Fig. 1. Effect of papaverine and intensain on volume velocity of cerebral blood flow. On left: excretion curve of xenon-133. Abscissa, time (in min); ordinate, rate of counting radioactivity on a logarithmic scale. Right: volume velocity of cerebral blood flow (in ml/100 g/min) in control experiments and after injection of papaverine (2 mg/kg) and intensain (10 mg/kg). C: control; I: intensain; P: papaverine.

All arteries supplying blood to the extracerebral tissues of the brain were ligated along the course of the blood before entering the brain. The resulting excretion curve of xenon-133 is the sum of two exponential curves. The first exponential curve reflects the blood flow in the blood vessels of the brain, the second the blood flow in the vessels of the soft tissues of the head [1]. After logarithmic plotting of the excretion curves and subtraction of the second curve from the first (Fig. 1), the half-elimination period ($T\frac{1}{2}$) was determined and used to calculate the cerebral blood flow (CBF) by the equation:

$$MK = K \times 100 \times 0.8 \text{ ml/100 g/min}$$

where K equals 0.693 $T\frac{1}{2}$ and 0.8 is the partition coefficient of xenon in a blood–tissue mixture.

To detect the vascular component in the action of the pharmacological agents on the cerebral hemodynamics, in the experiments of series II on cats a multichannel perfusion pump (resistograph) was used to record the resistance to the blood flow in the arterial systems supplying blood to the brain. For this purpose one of the channels of the resistograph was used for perfusion of the right and left maxillary arteries. The two vertebral arteries were perfused by the second channel. The extracranial vessels were carefully ligated.

Papaverine in a dose of 2 mg/kg and intensain in a dose of 10 mg/kg were used for the tests. The drugs were injected into the femoral vein or, in certain series of experiments, into the maxillary and vertebral arteries.

EXPERIMENTAL RESULTS AND DISCUSSION

The mean volume velocity of the cerebral blood flow of the dogs measured by the xenon method was 84 ± 5 ml/100 g/min, in agreement with data in the literature. Papaverine led to a marked decrease in the half-excretion time of the indicator, i.e., to an increase in the intracranial blood flow. The increase in the blood supply to the brain took place immediately after injection of the substance and its mean value was 44 ± 7.4% (Fig. 1). The cerebral blood flow in most experiments 10 min or more after injection of papaverine did not exceed the initial level. In all experiments an increase in the volume velocity of the cerebral blood flow was accompanied by a marked decrease in the systemic arterial pressure.

Intensain, injected intravenously in a dose of 10 mg/kg, also led to a marked decrease in the half-elimination time of xenon-133, reflecting an increase in the intracranial blood flow. The mean blood supply to the brain was increased by 50 ± 13% (Fig. 1). In all the experiments changes in the cerebral circulation were accompanied by a decrease in the level of the arterial pressure. In some experiments an increase in the cerebral blood flow was observed during the first minutes after injection of the drug, while in the rest the maximal increase in the blood flow was observed 10-45 min after injection of intensain.

The experiments using the technique of separate bilateral perfusion of the maxillary and vertebral arteries showed that papaverine, injected intravenously in a dose of 2 mg/kg, led to a marked decrease in tone of the maxillary and vertebral arteries. The resistance to the blood flow in the system of the maxillary arteries was reduced by 27 ± 2.8% after injection of papaverine, while the decrease in tone of the vertebral arteries was 28 ± 2.2% of its initial level. Meanwhile the arterial pressure was lowered on the average by 56 ± 3% below the control value. The original state of the tone of the maxillary and vertebral arteries was restored 5-10 min after injection of the drug.

Intensain, when injected intravenously in a dose of 10 mg/kg, led to a less marked decrease in resistance of the brain vessels to the blood flow. Under the influence of intensain the tone of the maxillary arteries was lowered by 13 ± 1.75%, whereas the resistance in the system of the vertebral arteries was lowered by only 7 ± 1.6% ($P < 0.05$) compared with its initial level. The arterial pressure was lowered by 35 ± 3.6%. In some experiments the tone of the cerebral arteries was restored 5-10 min after injection of the drug, while in others the duration of action of intensain reached 30 min or more.

Experiments using the method of resistography thus showed that the changes in the cerebral hemodynamics under the influence of these two drugs were due primarily to their direct action on the brain vessels. Evidence in support of this conclusion was given by a special series of experiments in which papaverine (0.5 mg) and intensain (4 mg) were injected directly into the maxillary or vertebral arteries. These experiments showed that both papaverine and intensain in most experiments led to selective dilatation of the cerebral vessels on the side of injection of the drug.

This investigation showed that both papaverine and intensain caused a marked increase in the cerebral blood flow, with an accompanying decrease in tone of the brain vessels. It is important to note, however, that whereas papaverine acts equally on the various vascular regions of the brain, intensain has a stronger action on the maxillary vessels and causes a correspondingly smaller decrease in the resistance in the vertebral arterial system. These results indicate that the intracranial vessels responsible for supplying blood to the cerebral hemispheres differ in their sensitivity to intensain from those supplying blood to the medulla and pons.

LITERATURE CITED

1. T. M. Darbinyan, K. D. Kalantarov, and B. I. Khersonskii, Éksper. Khir., No. 1, 54 (1971).
2. K. D. Kalantarov, Yu. M. Varentsov, and F. M. Lyass, Med. Radiol., No. 8, 19 (1966).
3. K. D. Kalantarov, and G. A. Oreshina, Novosti Med. Tekhniki, No. 2, 18 (1966).
4. L. I. Ostroumova, Farmakol. i Toksikol., No. 3, 278 (1969).
5. A. S. Saratikov, L. A. Usov, and L. I. Gol'd, Farmakol. i Toksikol., No. 2, 152 (1969).
6. K. Hoedt-Rasmussen, E. Sveinsdottir, and N. A. Lassen, Circulat. Res., 18, 237 (1966).
7. N. W. Jayne, G. P. Scheiberg, M. Rich, et al., J. Clin. Invest., 31, 111 (1952).
8. N. A. Lassen, K. Hoedt-Rasmussen, S. C. Sorensen et al., Neurology (Minneapolis), 13, 719 (1963).
9. J. S. Meyer, S. Ishikawa, and T. K. Lee, J. Neurosurg., 21, Part 1, 524 (1964).
10. N. A. Shenkin, J. Appl. Physiol., 3, 465 (1951).
11. J. C. De Valois and P. C. Peperkamp, Arch. Internat. Pharmacodyn., 189, 390 (1971).