EFFECT OF PIPOLPHEN (PROMETHAZINE) ON TONE OF THE INTRACRANIAL AND EXTRACRANIAL VESSELS AND THE GENERAL ARTERIAL PRESSURE

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UDC 612.824+612.143].014.46:615.2182

Intravenous and intracarotid injection of pipolphen reduced the tone of the intracranial and extracranial vessels, the response of the latter being stronger. The general arterial pressure was reduced following intravenous injection of the compound. Intravenous injection of pipolphen considerably weakened or completely abolished the action of histamine on the cerebral vessels and on the general arterial pressure.

Endogenous histamine plays an important role in the pathogenesis of disturbances of the cerebral circulation accompanied by headache [5]. For this reason antihistamine compounds, the most active of which is pipolphen [4], are therefore of great practical importance. Some workers [2, 9] have obtained good results from the use of pipolphen in the combined treatment of disturbances of the cerebral circulation. The pharamcological properties of promethazine has been studied in detail by Liberman [3].

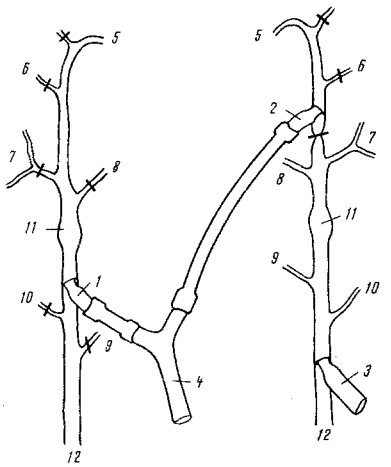

Fig. 1. Diagram of ligation of cranial vessels of a cat for parallel autohemoperfusion of intracranial and extracranial vessels. 1, 2, 4) Cannulas and three-day tube for perfusion of intracranial vessels; 3) cannula for perfusion of extracranial vessels; 5) branch of internal maxillary artery supplying brain; 6, 7, 8, 9-10) extracranial branches of carotid arteries; 11) carotid sinus; 12) common carotid artery.

In the investigation described below the effect of this substance on the tone of the cerebral vessels was studied.

EXPERIMENTAL METHOD

Acute experiments were carried out on 34 adult cats weighing 2-3.5 kg, anesthetized with chloralose and urethane (0.04 and 0.6 g/kg respectively) and under controlled respiration.

The tone of the intracranial and extracranial vessels was recorded by the autoperfusion method [7], by means of a two-channel resistograph. To prevent a collateral blood flow, the cerebral vessels were ligated as described in the literature [1, 6], with slight modifications enabling parallel recordings to be made of the tone of the intracranial and extracranial vessels. For this purpose, all branches of the carotid artery supplying the soft tissues of the head (muscles, skin), except branches of the internal maxillary artery supplying the brain, were ligated unilaterally. On the other side, the external carotid artery was ligated distally to the point where it gives off its main extracranial

Department of Pharmacology, Semipalatinsk Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 69, No. 6, pp. 54-57, June, 1970. Original article submitted October 27, 1969.

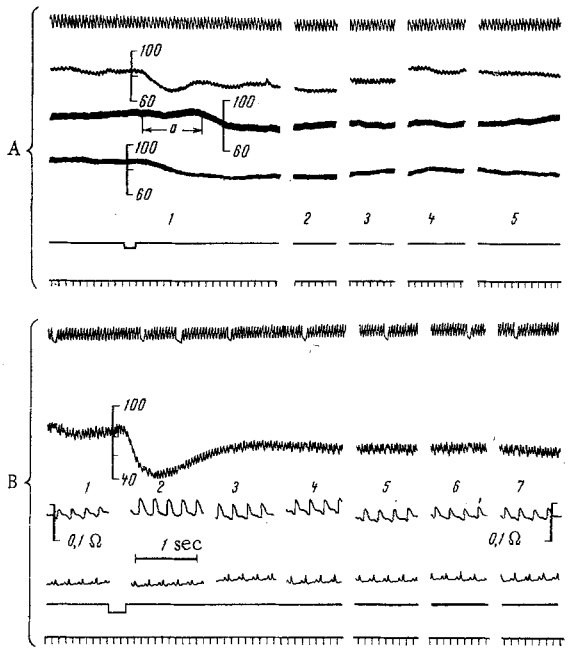

Fig. 2

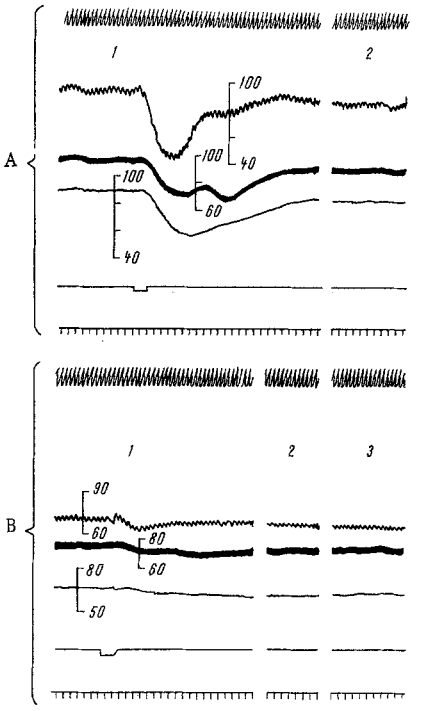

Fig. 3

Fig. 2. Effect of intravenous injection of pipolphen on tone of cerebral vessels and general arterial pressure. A) Results of resistography. From top to bottom: respiration (controlled); general arterial pressure; resistogram of intracranial vessels (interval a is the result of deliberate increase in volume of perfusion system); resistogram of extracranial vessels; marker of injection of drug (1 mg/kg); time marker 5 sec; 1) time of injection of drug; 2, 3, 4, 5) 5, 10, 20, and 40 min respectively after injection; B) results of rheoencephalography. From top to bottom: respiration (controlled); general arterial pressure; REG; ECG; marker of injection of compound (2 mg/kg); time marker 5 sec; 1) before injection of drug; 2, 3, 4, 5, 6, 7) 1, 2, 3, 5, 10, and 20 min respectively after injection.

Fig. 3. Effect of histamine on tone of cerebral vessels and general arterial pressure before and after injection of pipolphen in a dose of 3 mg/kg. A) Action of histamine (10 μg/kg, intravenously) before injection of pipolphen; B) action of same dose of histamine 20 min after injection of pipolphen; 1) time of injection of histamine; 2, 3) 5 and 10 min after injection. Remainder of legend as in Fig. 2A.

branches, which were not ligated (Fig. 1). The intracranial vessels were perfused through a three-way tube (4) connected to cannulas (1 and 2); the extracranial vessels through the cannula (3). The common inlet to the channels of the resistograph was connected to the central end of the common carotid artery.

In a separate series of experiments the method of rheography of the skull was used. Using orbital and occipital electrodes, the rheoencephalogram of the animals was taken by means of a single-channel RG1-01 rheograph connected to a two-channel electrocardiograph. The ECG in standard lead II was recorded parallel with the REG. While these recordings were made, the artificial respiration apparatus was temporarily switched off (for 4-6 sec).

Pipolphen was injected intravenously as a 0.25-0.5% solution in doses of 0.5-3 mg/kg and intra-arterially (by the intracarotid route) in doses of 0.05-0.1 mg/kg. Working solutions were made up from the 2.5% official ampule solution of Hungarian manufacture.

EXPERIMENTAL RESULTS

The resistography experiments showed that intravenous injection of pipolphen in doses of 0.5-1 mg/kg lowers the tone of the intracranial vessels on the average by 18 ± 1.8% and of the extracranial vessels by 25 ± 3.7% and lowers the general arterial pressure by 36 ± 5.7%. The action occurred immediately after injection of the drug and continued for about 20 min. After intravenous injection of pipolphen in doses of 2-3

mg/kg, the tone of the intracranial vessels was lowered by 26 ± 4.2%, and of the extracranial vessels by 29 ± 5.2%, and the general arterial pressure fell by 40 ± 3.2%. This effect began immediately after injection of the drug and was prolonged. In most experiments the level of the perfusion and general arterial pressure remained below its initial value until the end of the experiment (more than 60 min).

Lowering of the general arterial pressure is known to reduce the tone of the cerebral vessels regardless of the cause of the general hypotension. Consequently, after administration of hypotensive preparations, an indirect reaction of the cranial vessels may occur in response to the change of arterial pressure, together with a direct response to the effect of the compound on the vessel walls.

By means of resistography it is possible to distinguish between direct and indirect effects of pharamacological agents on blood vessels [8]. The use of this method in some experiments showed that pipolphen exerts mainly a direct action on the vessels. The delay in the response (interval a) of the intracranial vessels following a deliberate increase in the volume of the corresponding perfusion canal can be seen in Fig. 2A. Similar results were obtained in other experiments by an increase in the volume of the perfusion canal connected to the extracranial system of blood vessels of the head.

Other evidence of the predominantly direct action of pipolphen on the cerebral vessels was given by experiments in which the drug was injected into the carotid artery: injection of pipolphen in doses of 0.05-0.1 mg/kg into the perfusion system of the intracranial vessels lowered the resistance of these vessels by 21 ± 2.7%. The resistance of the extracranial vessels and the general arterial pressure were not significantly changed. Following injection of the same doses of the drug into the perfusion system of the extracranial vessels, their resistance was reduced by 31 ± 5.4%. The resistance of the intracranial vessels and the general arterial pressure likewise were not significantly changed under these conditions. The response of the cerebral vessels to pipolphen was not abolished by preliminary atropinization of the animals. In the rheoencephalography experiments, pipolphen in doses of 1-2 mg/kg increased the amplitude of the rheographic wave by 68 ± 4%. The general arterial pressure was lowered under these conditions by 39 ± 5.8%. The increase in amplitude of the REG and lowering of the general arterial pressure took place immediately after injection of the drug and were most marked during the first and second minutes (Fig. 2B). The duration of these changes was 10-30 min. Besides an increase in amplitude of the rheographic wave, in some experiments the apex of the wave also became pointed (if it was rounded before injection of the drug), and the dicrotic notch was diplaced downward.

According to data in the literature changes in the REG of this type indicate lowering of the tone of the cerebral vessels and an increase in their blood volume.

Having regard to the antihistamine properties of pipolphen, it was decided to study to what extent this compound can abolish the characteristic histamine effect on the cerebral vessels. Experiments showed that intravenous injection of pipolphen in doses of 2-3 mg/kg considerably reduced or completely abolished the action of histamine on the cerebral vessels and general arterial pressure (Fig. 3).

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