

PHARMACOLOGY

EFFECT OF p-AMINOBENZOIC ACID ON THE COURSE OF EXPERIMENTAL MYOCARDIAL INFARCTION

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UDC 616.127-005.8-092.9-085.752.6

One of the more important problems facing modern pharmacology is the search for substances capable of restoring the circulation of the heart in myocardial infarction. Improvement in the coronary circulation may be obtained both by a direct coronary-dilator effect on the vessels of the heart and by influences acting on metabolic processes and the hemodynamics in the heart muscle [3]. From this point of view there is considerable interest in procaine [8] and the product of its hydrolysis — p-aminobenzoic acid (PABA), an active component of procaine, taking part in intimate biochemical processes and possessing a well-defined antihistamine action [1, 6].

The object of the present investigation was to study the effect of PABA on the course of experimental myocardial infarction in animals.

EXPERIMENTAL METHOD

Myocardial infarction was produced in the animals by ligating the descending branch of the left coronary artery and vein in their upper third with a silk ligature. Operations by this method were performed on 45 rabbits and 10 dogs. In all the animals the electrocardiogram (ECG) was recorded before the operation in standard and chest leads, and clinical and laboratory investigations were carried out. The arterial pressure was measured in the common carotid artery, exteriorized into a skin flap on the neck.

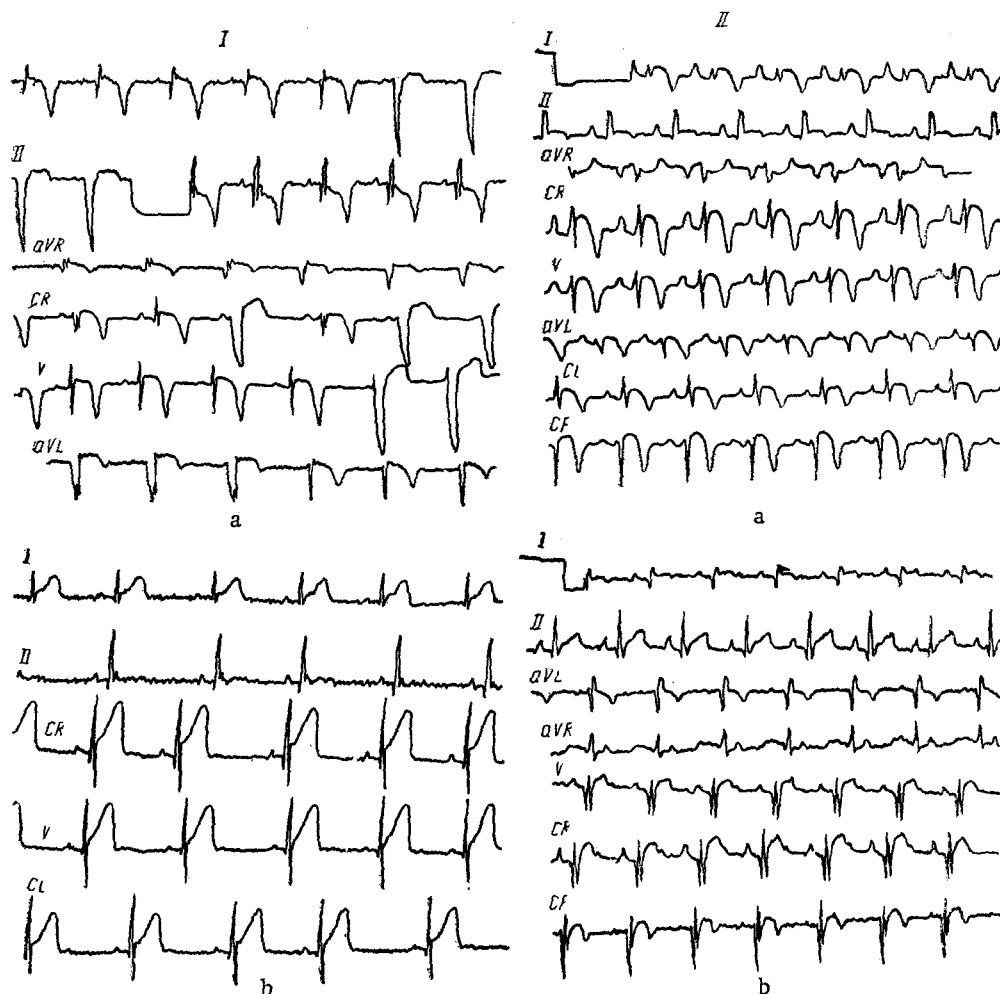
EXPERIMENTAL RESULTS AND DISCUSSION

The series of experiments were carried out.

The experiments of series I were the controls (20 rabbits and 5 dogs). The experiments lasted for between 2 days and 3-6 weeks. In all the animals an acute infarct developed 24 h after ligation of the vessels, as confirmed by the ECG findings and the results of clinical and laboratory investigations (poor general condition, high leukocytosis: in the rabbits up to 25,000-27,000 and in the dogs up to 18,000-20,000/mm³; a high ESR: 27-31 and 33-45 mm in 1 h respectively; and a marked shift of the leukocyte formula to the left).

The changes in the ECG developing in the rabbits and dogs with an acute myocardial infarct in various localizations are shown in the figure. Disturbances of the rhythm were observed, with multiple grouped ventricular extrasystoles, changes in the first and last parts of the ventricular complex, and lesions of the conducting system of the heart. In both the standard and the chest leads to the EEG the voltage of the R waves was reduced or they disappeared completely, while the S — T₁₋₂ intervals were raised very high above the isoelectric line, and changed into typical coronary T waves. Deep and wide QS waves appeared in the chest leads, indicating a necrotic lesion of the myocardial muscle. These changes in the ECG of the animals of the control group persisted for 3-6 weeks in the dogs and for between 4 weeks and 3 months in the rabbits. The control animals were sacrificed at the same time as the experimental animals, at different periods of the experiment. The heart was fixed in 10% formalin solution. Sections of the material embedded in paraffin wax were stained with hematoxylin-eosin, by Van Gieson's method, by Heidenhain's iron-hematoxylin, and by Mallory's method. Two weeks after the development of the acute myocardial infarct, at necropsy on most of the animals of the control group multiple adhesions were found macroscopically between the pericardium and the adjacent organs as the result of the development of pericarditis. Macroscopic examination of the heart preparations showed foci of necrosis in various places and of different degrees of maturity, measuring up to 2.5 × 1.2 cm. The heart of most dogs was flabby, with greatly dilated chambers and thin walls, while in 15% of cases an aneurysm had developed at the site of the infarct.

Department of Pharmacology, Leningrad Chemo-Pharmaceutic Institute (Presented by Active Member of the Academy of Medical Sciences of the USSR S. V. Anichkov). Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 63, No. 4, pp. 61-64, April, 1967. Original article submitted May 29, 1965.



Changes in the ECG of dogs with myocardial infarction after treatment with p-aminobenzoic acid (I) and in the control (II). a) After 48 h; b) on the 10th day.

On histological investigation of the preparations of the hearts taken from the rabbits and dogs of the control group, typical cellular infiltration was most commonly observed, with varying degrees of differentiation of the cells. Alternation of young connective tissue with areas of necrotic, fragmented, and swollen muscle fibers, which had lost their cross-striation, was observed and in some parts of the myocardium, proliferation of connective tissue, some of it more mature, was found.

The animals of series II (25 rabbits and 5 dogs) with an acute myocardial infarct received subcutaneous injections of PABA in doses of 12-15 mg/kg daily, twice a day throughout the period of observation. Examination of the electrocardiographic, clinical, and laboratory findings for the rabbits and dogs treated with PABA (12 mg/kg) on the second day showed restoration of the normal rhythm with disappearance of the extrasystoles, an increase in the voltage of the waves, and some reduction in the depth of the QS waves, evidently as a result of improvement of the coronary circulation. The leukocyte count was high ($25,700/\text{mm}^3$), but the ESR of the rabbits had fallen to 11 mm in 1 h (compared with 31 mm). On the 5th day an increase in the voltage of the positive waves was observed on the ECG of the rabbits, and R waves had appeared in both the standard and the chest leads, with disappearance of the pathological QS complexes. The general condition of three of the dogs was very much improved at these times, and the leukocyte count had fallen to 10,400 (compared with 24,750); the ESR was 28 mm in 1 h and the blood pressure slightly lowered - to 85 mm. The waves and complexes in all standard leads of the ECG had returned to normal. In the chest leads, on the other hand, deep pathological Q waves, up to 12 mm in depth, with well marked negative T waves remained. On the 9th-14th day, in 85% of the animals (receiving 12 mg/kg PABA) the ECG and results of the clinical and laboratory investigations were normal, while in the remaining 15% of animals, organization of the myocardial infarct took place on the 16th-18th day.

Two other dogs – Al'ma and Murzik – received PABA by subcutaneous injection in a dose of 15 mg/kg on the 2nd day after a high ligation of the coronary artery accompanied by the development of an extensive anterior infarct with typical changes in the ECG and a block of the anterior branch of the bundle of His. Before treatment, the condition of these animals was extremely grave, for they showed signs of severe anoxia and marked blood changes (ESR 42 mm in 1 h, leukocyte count 23,250). On the 2nd day after the injection of PABA the rhythm was normal again and the ventricular extrasystoles had disappeared. On the 5th day the animals' condition was much improved and they took their food eagerly, their respiration was smooth, the volume and tension of the pulse was good (rate 124 beats/min) and their arterial pressure had risen to 95 mm; the ESR had fallen to 13 mm in 1 h (compared with 42 mm in 1 h) and the leukocyte count to 20,800. Considerable improvement in the ECG was found in the standard leads. On the 12th day the normal ECG was restored in all leads for the dogs treated with PABA. The animals were sacrificed after the ECG and the results of the clinical and laboratory tests had returned to normal.

At postmortem examination of the heart preparations of most of the experimental rabbits and dogs no adhesions were found between the pericardium and the adjacent organs. The pericardium was easily stripped and shining, the heart chambers were not dilated, the heart muscle was juicy, and bright red in color. Individual areas of former necrotic foci in the myocardium were in a state of organization; their mean size in the rabbits was 0.8-0.5 cm and in the dogs 1.2×0.8 cm, i.e., 50-60% smaller than in the controls. In all preparations of the heart the coronary vessels were considerably dilated.

The development of connective tissue of varying degrees of maturity was observed histologically at the sites of former necrotic foci. Special attention was drawn to the well marked vascularization both in the areas of connective scar tissue and throughout the myocardium, mainly as a result of dilatation of the capillaries and an increase in the number of arteries, and also to the absence of necrosis in the perifocal zone.

In acute experiments on cats (by N. V. Kaverina's method) a constant and well marked coronary-dilator effect was observed in response to injection of PABA (15-20 mg/kg), as shown by a considerable increase in the volume velocity of the coronary blood flow (by 80-108%) and also by a distinct reduction in the oxygen consumption of the heart.

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