EFFECT OF LIDOCAINE AND PYROMECAINE ON THE SIZE OF AN EXPERIMENTAL MYOCARDIAL INFARCT

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Myocardial infarction as a rule is accompanied by marked disturbances of the cardiac rhythm. When antiarrhythmics are used in the treatment of such patients, it is therefore very important to take into account not only their specific antiarrhythmic properties, but also their anti-ischemic action, which may limit the size of the focus of necrosis in the heart muscle.

The aim of this investigation was to compare the effect of the new Soviet antiarrhythmic agent pyromecaine and the known antiarrhythmic lidocaine on the size of an experimental myocardial infarct (MI).

EXPERIMENTAL METHOD

Experiments were carried out on 42 noninbred male rats weighing 180-200 g. Under superficial ether anesthesia the left coronary artery was ligated in the animals 4-5 mm from its origin [12]. The animals' ECG was recorded in three standard leads. Recordings were made before occlusion of the coronary artery, 5 min after occlusion, and before sacrifice of the animals. The rats were killed 72 h after the operation. The MI was revealed macrohistochemically with the aid of nitro-BT. A mathematical model, used previously in experiments on rats [15], was used to calculate the size of the focus of necrosis [8]. Lidocaine and pyromecaine were injected intraperitoneally in accordance with the following scheme: in a dose of 2.0 mg/kg 15 min before occlusion of the coronary artery, immediately after occlusion, and then every hour for 3 h. On the 2nd and 3rd days a dose of 3.0 mg/kg was given twice daily. The drug used for comparison was propranolol, which was injected in a sessional dose of 1.0 mg/kg 15 min before and 2 h after occlusion of the coronary artery. On the 2nd and 3rd days a dose of 1.0 mg/kg was given twice a day. In the control series the animals received the equivalent volume of physiological saline. The results were subjected to statistical analysis. The significance of the differences was determined by Student's t test for unpaired samples and with a level of significance of $P = 0.05$ [2]. To judge the effect of the drugs on the blood supply to the focus of myocardial ischemia experiments were carried out on 10 dogs of both sexes weighing 10-15 kg, anesthetized with pentobarbital (40 mg/kg, intravenously), with an open chest and artificial ventilation. The method of alternate recording of the volume velocity of of the retrograde blood flow and the retrograde pressure in the distal segments of the anterior descending branch of the left coronary artery, ligated in its middle third, was used. The retrograde blood flow was recorded by means of an intervalograph. At the same time, using an MFV-1200 electromagnetic blood flowmeter (Nihon Kohden, Japan) the volume velocity of the blood flow was measured in the circumflex branch of the left coronary artery, which supplies blood to intact regions of the myocardium. With this technique it was possible to judge the redistribution of the blood flow between the intact and ischemic regions of the myocardium [6, 14]. The systemic blood pressure (in the carotid artery) and parameters of the blood supply to the heart were recorded on a "Mingograf-81." Lidocaine and pyromecaine were injected intravenously in a dose of 2.0 mg/kg. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Within a few minutes after occlusion of the left coronary artery marked ischemic changes were observed in the rats: in standard derivations of the ECG the ST segment was considerably

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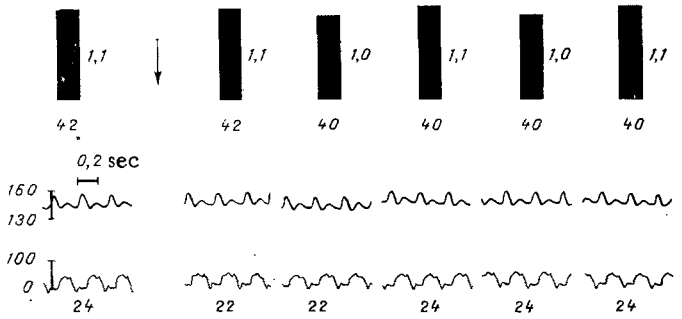

Fig. 1. Effect of lidocaine (2.0 mg/kg, intravenously) on blood supply to the ischemic myocardium of a dog. From top to bottom: Retrograde blood flow in territory supplied by ligated anterior descending branch of left coronary artery (in ml/min); retrograde perfusion pressure (in mm Hg); systemic blood pressure in carotid artery (in mm Hg); blood flow in circumflex branch of left coronary artery (in ml/min). From left to right: before injection, 5, 10, 20, 30, and 45 min after injection of lidocaine (arrow).

elevated and the T wave enlarged. Later, 3 days after occlusion of the coronary artery, signs of developing myocardial infarction were observed on the ECG: as a rule, a QS complex or deep Q wave was observed.

The antiarrhythmics tested reduced the size of the focus of myocardial necrosis significantly. Whereas in the control series of experiments the volume of MI was 35.7 ± 2.7% of the total volume of the left ventricle, under the influence of lidocaine it decreased to 20.1 ± 1.8%, and of pyromecaine to 23.7 ± 3.3% ($P < 0.05$). The comparison drug, propranolol, also reduced the size of MI. The volume of the focus of necrosis in this series of experiments was 23.8 ± 2.6% ($P < 0.05$) of the total volume of the left ventricle.

Recent investigations on various species of experimental animals (rats, dogs, etc.) have shown that after occlusion of the coronary artery a boundary zone of ischemic damage exists in the heart [9, 10, 13]. By acting on this zone with various drugs (β-adrenoblockers, nitroglycerin, calcium ion antagonists, etc.) the size of an experimental MI can be reduced [1, 3, 15]. This effect of the drugs is based on different mechanisms: an increase in blood supply to the ischemic focus due to improvement of the collateral circulation or redistribution of the blood flow in the myocardium in favor of the ischemic zone, a decrease in the oxygen consumption of the heart, stabilization and prevention of changes in permeability of cell membranes, and so on [10].

To what can the decrease in size of MI under the influence of the drugs studied be attributed? Experimental investigations have shown that an important mechanism in the beneficial action of propranolol on the size of a focus of necrosis in the heart is its ability to redistribute the blood flow in the heart muscle and to improve the blood supply actually in the ischemic zone [14]. In view of these data it was interesting to study the role of this factor in the action of the antiarrhythmic drugs tested.

Experiments on dogs showed that lidocaine and pyromecaine, after occlusion of the descending branch of the left coronary artery, have a very weak (not significant) effect on the blood supply to the myocardium and do not redistribute the blood flow in the heart muscle in favor of the ischemic focus. For instance, 10 min after injection of lidocaine, when the effect of the drug on the hemodynamics is maximal, the volume velocity of the retrograde coronary blood flow and of the blood flow in the circumflex branch of the left coronary artery, supplying blood to intact zones of the myocardium, were virtually indistinguishable from the control. The average decrease was 5.5 ± 9 and 3.9 ± 4.2%, respectively ($P > 0.1$; Fig. 1). In a series of experiments with pyromecaine, at the 10th minute after injection of the drug these values also were not changed statistically significantly: the decrease was 12.5 ± 5.3 and 17.3 ± 8.4%, respectively ($P > 0.05$). The antiarrhythmics caused virtually no change in either the systemic or the retrograde perfusion pressure.

The decrease in size of the experimental MI due to lidocaine and pyromecaine is thus evidently not connected with their effect on the blood supply to the ischemic zone. The drugs do not redistribute the blood flow in favor of the ischemic focus. This is shown by the fact that

the retrograde inflow of blood to the ischemic zone was changed under their influence by the same degree as the blood flow in the intact zones of the heart muscle. Our data so far as lidocaine is concerned are in agreement with the observations of other workers, who with the aid of labeled microspheres, showed that limitation of the size of an MI in dogs due to this drug is unconnected with its effect on the blood supply to the ischemic zone [11].

One possible mechanism of the limitation of the size of MI through the action of the antiarrhythmic drugs studied may be their influence on ionic permeability of cell membranes. It is well known that the local anesthetics lidocaine and pyromecaine have considerable membrane-stabilizing properties [4, 5, 7]. By reducing the pathological exchange of electrolytes induced by ischemia, and by maintaining ionic homeostasis at a certain level, lidocaine and pyromecaine can create conditions more favorable for viability of cardiomyocytes injured by ischemia.

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