EFFECT OF THE NEW ANTIARRHYTHMIC DRUG BONNEKOR ON HEMODYNAMICS AND ACTIVITY OF THE ISCHEMIC HEART

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The antiarrhythmic and antifibrillatory properties of the new drug bonnekor, synthesized as a result of collaboration between the Institute of Pharmacology, Academy of Medical Sciences of the USSR, and the "Germed" State Enterprise (East Germany), have now been well studied [7, 8]. Meanwhile the effect of bonnekor on the hemodynamics and function of the heart, especially under conditions of coronary circulation insufficiency, remains inadequately studied. The investigation described below was carried out to remedy this defect. It was decided to study the drug from the comparative aspect, with the known antiarrhythmic agents ethacizine and lidocaine.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male rats weighing 250-300 g, anesthetized with pentobarbital sodium (40 mg/kg, intraperitoneally), and artificially ventilated. The blood pressure in the carotid artery was recorded by means of a micromanometer [3]. An ultrasonic transducer, calibrated in units of volume velocity of blood flow (internal diameter 2.5 mm) [2], was placed on the ascending part of the arch of the aorta. The linear velocity of the blood flow and cardiac output were measured. Myocardial contractility was estimated by electronic differentiation of the cardiac ejection curve, and the stroke volume was determined by electronic integration of this curve. The power of the heart was determined by means of an analog computer as the product of pressure in the carotid artery (in mm Hg) and the pulse blood flow in the ascending aorta (in ml/min). Parameters were recorded on the H3031 instrument. Ischemia was induced by ligation of the descending branch of the left coronary artery by Litvitskii's method [7]. The drugs were injected 2 min before occlusion of the coronary artery in the following doses: bonnekor and ethacizine 0.5 and 1 mg/kg, lidocaine 2 and 5 mg/kg in a volume of 0.3 ml in the course of 3 min. In the control series of experiments physiological saline was injected in accordance with the same schedule. The results were subjected to statistical analysis by Student's t test. Altogether 50 rats were used.

EXPERIMENTAL RESULTS

As the control series of experiments showed, occlusion of the coronary artery in rats leads to a fall of the systemic blood pressure, reduction of the stroke volume and cardiac output, and reduction of contractility and power of the heart (Fig. 1a). Prophylactic injection of bonnekor in a dose of 0.5 mg/kg under these conditions largely prevents changes in the hemodynamics and cardiac activity: the systemic blood pressure was lowered and the stroke volume and cardiac output reduced by a less marked degree than in animals of the control series of experiments (Figs. 1 and 2). The ability of the drug to prevent a sharp fall in contractile function of the heart muscle is very important. For instance, whereas in the control series of experiments contractility of the myocardium and its power were reduced immediately after occlusion of the coronary artery, and this effect gradually increased with time, after administration of bonnekor these parameters showed much smaller changes and they were virtually the same as the initial values (Fig. 3).

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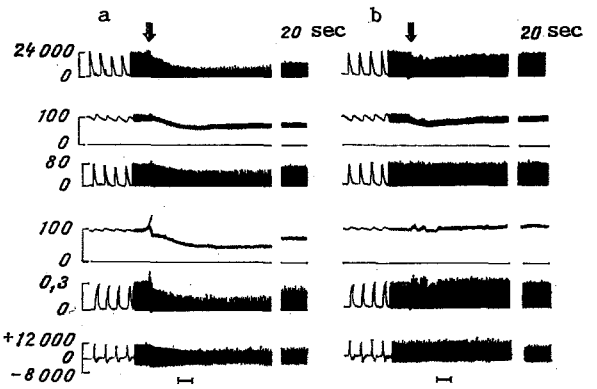

Fig. 1. Effect of bonnekor (0.5 mg/kg, intravenously) on hemodynamics and cardiac activity of rats after coronary artery occlusion. a) Control, b) after administration of bonnekor. Arrow indicates beginning of occlusion. From top to bottom: power of the heart (mm Hg· ml/min), blood pressure (mm Hg), linear velocity of blood flow in ascending aorta (cm/sec), cardiac output (ml/min), stroke volume (ml), and myocardial contractility (cm/sec^2). Time scale 10 sec.

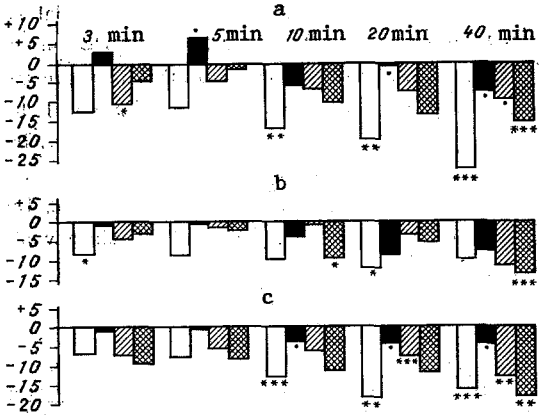

Fig. 2. Effect of bonnekor (0.5 mg/kg), ethacizine (0.5 mg/kg), and lidocaine (2 mg/kg) on systemic blood pressure (a), stroke volume (b), and cardiac output (c) in anesthetized rats with acute coronary insufficiency. Here and in Fig. 3: ordinate, changes in parameters, % of initial level; abscissa, duration of occlusion; unshaded columns — control, black — bonnekor, obliquely shaded — ethacizine, cross-hatched — lidocaine; *p < 0.05, **p < 0.02, ***p < 0.01 compared with initial level. ˙p < 0.05, ˙˙p < 0.02, ˙˙˙p 0.01 compared with control.

Ethacizine (0.5 mg/kg) and lidocaine (2 mg/kg) also largely prevented changes in the hemodynamics and cardiac activity after coronary arterial occlusion (Figs. 2 and 3). However, bonnekor prevented changes in cardiac activity caused by coronary arterial occlusion by a greater degree than ethacizine or lidocaine (Fig. 3).

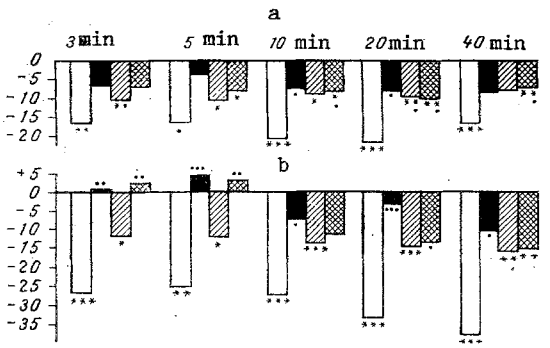

Fig. 3. Effect of bonnekor (0.5 mg/kg), ethacizine (0.5 mg/kg), and lidocaine (2 mg/kg) on contractility (a) and power of the heart (b) in anesthetized rats with acute coronary insufficiency.

It is important to note that with an increase in the doses of the drugs (bonnekor and ethacizine to 1 mg/kg, lidocaine to 5 mg/kg) their protective action on the hemodynamics and cardiac activity was not exhibited under conditions of acute coronary arterial occlusion: the cardiac output, and contractility and power of the heart showed the same changes in these experiments as in the control series. However, bonnekor produced significant bradycardia (decrease of 12.3 ± 1.4% in the heart rate, $p < 0.05$ compared with the control, at the 10th minute of occlusion), by contrast with ethacizine and lidocaine. The systemic arterial pressure remained virtually at its initial (background) level, whereas the drugs used for comparison lowered it (by 16.9 ± 2.8% by ethacizine at the 10th minute of occlusion, by 11.4 ± 2.5% by lidocaine compared with the control; $p < 0.01$).

Disturbances of the hemodynamics and cardiac function in myocardial ischemia may be largely due to the onset of cardiac arrhythmias. By its action directly on the cardiomyocyte membrane, bonnekor, like ethacizine and lidocaine, reduces the electrical instability of the myocardium, thus reducing the severity and frequency of onset of cardiac arrhythmias. Our observations showed that during ischemia treated by the antiarrhythmic drugs studied, if disturbances of the cardiac rhythm should arise, they were solitary and not multiple or burst-like in character.

Of the known antiarrhythmic agents, including lidocaine and phenothiazine derivatives, bonnekor is the one most capable of protecting the heart against sympathetic influences during the period of myocardial ischemia [1]. It is this property of bonnekor which is linked with its high antifibrillatory activity [5, 6]. These properties of the drug evidently play an important role also in its positive effect on the hemodynamics and on activity of the heart muscle during ischemia.

Bonnekor, like the drugs used for comparison (ethacizine and lidocaine), depending on the dose used, can thus exert a favorable action on the hemodynamics and cardiac function in acute myocardial ischemia. From this point of view bonnekor has definite advantages over the drugs with which it was compared.

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