ELECTROPHYSIOLOGICAL ACTION OF ETHACIZINE IN ACUTE MYOCARDIAL ISCHEMIA IN DOGS

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The antiarrhythmic effectiveness of drugs with quinidine-like action in experimental myocardial ischemia depends essentially on the time of administration of the drugs relative to occlusion of the coronary artery. For instance, apridine and ethmozine effectively inhibit disturbances of rhythym in the late stage of experimental myocardial infarction (24 h after coronary artery occlusion) and promotes the development of arrhythmias and ventricular fibrillation in the period of acute occlusion of the coronary artery [1, 2, 4, 8, 12, 15]. Quinidine abolishes disturbances of rhythm in the late stage of myocardial infarction and increases the probability of development of ventricular fibrillation in acute myocardial inschemia [9] or does not affect it [8].

The new Soviet antiarrhythmic agent ethacizine (ethmozine diethylamine analog) has a powerful antiarrhythmic action in the late stage of experimental myocardial infarction, which is several times stronger and more prolonged than that of ethmozine [1].

The aim of this investigation was to study the effect of ethacizine on the probabiliy of development of ventricular fibrillation and on the processes of spread of excitation in the zone of ischemia after acute coronary artery occlusion in dogs. The pharmacokinetics of ethacizine after a single intravenous injection also was studied.

EXPERIMENTAL METHOD

Measurement of the Conduction Time of Excitation. Mongrel dogs weighing 10-20 kg were anesthetized with pentobarbital (30-35 mg/kg, intravenously) and artificially ventilated. Thoracotomy was performed through the third right intercostal space, and complete transverse heart block was induced by injection of 0.1-0.2 ml of 40% formalin solution into the region of the of the atrioventricular node [1]. The thorax was then closed by suture and reopened through the fourth left intercostal space. For repeated atraumatic occlusion a segment of the left-descending coronary artery was mobilized from the surrounding tissue for a distance of 1-2 cm from its origin. Three bipolar endocardial and three epicardial electrograms were recorded: One pair of electrodes was located outside the presumptive zone of ischemia, the other two inside it (in the region of bifurcation of the coronary artery) [4]. The cardiac rhythm was kept constant at 180 beats/min by stimulation of the right ventricle. Acute myocardial ischemia was induced by occlusion of the coronary artery for 5 min. After control occlusion and the recovery period, ethacizine in doses of 0.5 and 1 mg/kg was injected through a catheter into the femoral vein in the course of 3 min. Coronary artery occulsion was carried out 30, 90, 150, and 210 min after injection of the drug. To analyze the time course of electrocardiograms time intervals between application of the stimulus and appearance of the electrograms, and also their amplitude and duration were measured [4]. If ventricular fibrillation developed, defibrillation was carried out immediately after its appearance. The ECG in lead II and the blood pressure in the femoral artery were recorded throughout the experiment. All parameters were recorded on photographic paper with a winding speed of 150 mm/sec (VP-12 recorder, "Electronics for Medicine," USA).

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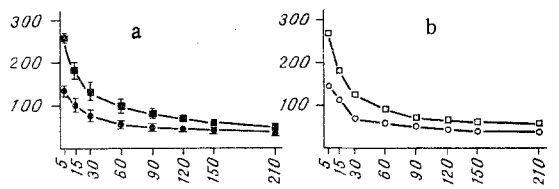

Fig. 1

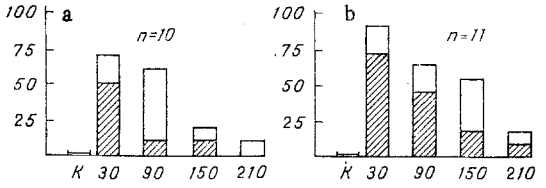

Fig. 2

Fig. 1. Dependence of plasma ethacizine concentration on time after a single intravenous injection. Abscissa, time after end of injection of drug (in min); ordinate, ethacizine concentration in blood plasma (in ng/ml). a) Intact dogs (M ± m, n = 4); b) dogs whose coronary artery was occluded for 5 min — 30, 90, 150, and and 210 min after injection of ethacizine.

Fig. 2. Effect of ethacizine in doses of 0.5 mg/kg (a) and 1 mg/kg (b) on development of ventricular fibrillation during acute occlusion of left descending coronary artery. Abscissa, time after end of injection of drug (in min); ordinate, percentage of animals developing ventricular fibrillation. Shaded part of columns indicates animals which developed ventricular fibrillation in period of coronary artery occlusion; unshaded part, during restoration of coronary blood flow. K) Control.

Determination of the Plasma Ethacizine. Experiments were carried out on dogs anesthetized with pentobarbital (30-35 mg/kg, intravenously). Blood was taken through a catheter in the jugular vein before injection and 5, 15, 30, 60, 90, 120, 150, and 210 min after intravenous injection of ethacizine in doses of 0.5 and 1 mg/kg. The heparinized blood was centrifuged for 10 min at 7000 rpm. Ethacizine was assayed quantitatively by means of a high-efficiency Varian-8500 liquid chromatograph, with MicroPac CN-10 column (USA). A Varian-635 ultraviolet spectrophotometer with wavelength of 254 nm was used as the detector. The mobile phase consisted of a mixture of heptane, isopropanol, methanol, and butylamine in the ratio of 35:65:1.6:0.15. The total rate of elution was 60 ml/h. The retention time of ethacizine was 4.4 min. At the extraction stage an internal standard was added to the plasma, in the form of the ethacizine analog, ethmozine (0.4 μg/ml). The retention time of ethmozine was 5.4 min. Extraction with 3 volumes of chloroform at pH 9.0 was repeated three times, for 3 min each time. The chloroform at pH 9.0 was removed by evaporation. The dry residue was dissolved in 150 μl of the mobile phase. From 10 to 50 μl was introduced into the chromatograph.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1a that the plasma ethacizine concentration in intact dogs fell quite quickly during the first 60 min after a single intravenous injection of the drug. Subsequently the concentration changed much more slowly. The half-elimination time of ethacizine was about 30 min, which is two or three times longer than the half-elimination time of quinidine-like drugs such as apridine and Mexitil [6, 12]. A similar change in the ethacizine concentration also was observed in dogs whose coronary artery was periodically occluded for 3.5 h (Fig. 1b).

Data on the effect of ethacizine on the appearance of ventricular fibrillation during acute myocardial ischemia are given in Fig. 2. It will be noted that in all the experiments in which fibrillation developed during the control occlusion, it always took place as well during occlusion following injection of ethacizine. Accordingly, only those experiments were included in the analysis in which ventricular fibrillation did not arise in the control during coronary artery occlusion or in the period of restoration of the coronary blood flow. For instance, 30 min after injection of 0.5 mg/kg of ethacizine, ventricular fibrillation occurred in 7 of the 10 dogs, but after injection of 1 mg/kg it developed in 10 of the 11 dogs in which fibrillation was not observed during the control occlusion (Fig. 1a).

Data on the effect of ethacizine on the amplitude, duration, and time of development of local electrograms are given in Fig. 3. The drug reduced the amplitude and increased the duration and the time of appearance of the electrograms. The effect of ethacizine was more marked in the subepicardial region of the ischemic zone. All parameters of the electrograms returned to the control values 210 min after injection of the drug. It will be noted that the time of development of the electrograms was equal to the time of spread of excitation from the stimulating electrodes, located in the right ventricle, to the recording electrodes, located in the zone of ischemia of the left ventricle. For the greater part of its path, excitation is con-

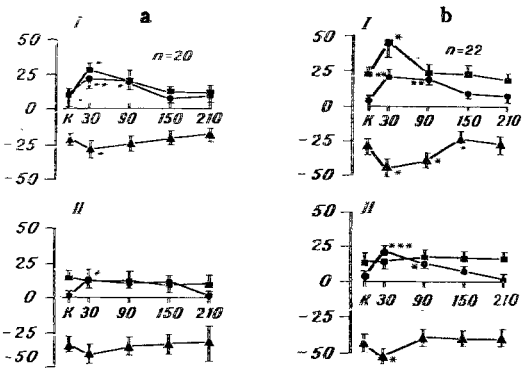

Fig. 3. Effect of ethacizine in doses of 0.5 mg/kg (a) and 1 mg/kg (b) on changes induced by ischemia in epicardial (I) and endocardial (II) electrograms of left ventricle (M ± m). Ordinate, relative changes in parameters of electrograms 3 min after beginning of coronary artery occlusion in control and after injection of drug, expressed as percentages of corresponding values obtained before coronary artery occlusion. Circles show changes in time from moment of application of stimulus to appearance of electrograms, squares show changes in duration of electrograms, and triangles show changes in amplitude of electrograms. *P < 0.05, **P < 0.01, ***P < 0.001 (t test for tied pairs was used). Remainder of legend as to Fig. 2.

ducted through myocardium outside the zone of ischemia. In the period of coronary artery occlusion the velocity of conduction of excitation through the intact myocardium remained unchanged. Therefore even the small increase in total conduction time (by 20%, for example, in the epicardial region after injection of 1 mg/kg of ethacizine) is evidence of a marked decrease in the velocity of spread of excitation in the ischemic zone under the influence of ethacizine.

Comparison of the results of the study of the pharmacokinetics of ethacizine and its electrophysiological effect in acute coronary artery occlusion shows that the decrease in the velocity of conduction of excitation in the zone of ischemia and the increase in the probability of ventricular fibrillation under the influence of ethacizine are proportional to its plasma concentration (Figs. 1-3).

Differences in the action of the antiarrhythmic drugs in the acute and late stages of myocardial infarction are probably due to differences in the mechanisms of the arrhythmias at these times of myocardial infarction. In the case of acute coronary artery occlusion one of the main electrophysiological changes is depolarization of the fibers of the ischemic myocardium [7, 11]. As a result the rate of rise of the front of the action potential is reduced, the conduction velocity is reduced, and conditions are created for the appearance of foci of circulation of excitation in the zone of ischemia [11, 14]. Quinidine-like drugs, inhibiting the fast inward sodium current, thus reduce the velocity of conduction of excitation and promote the development of disturbances of rhythm and ventricular fibrillation in acute myocardial ischemia [8, 12, 15]. Cardiac arrhythmias in the late stage of experimental myocardial infarction are linked with abnormal automaticity of the subendocardial Purkinje fibers, located in the zone of ischemia [10]. It has been shown that an essential role in the development and maintenance of this increased automatic activity is played by tetrodotoxin-sensitive fast sodium channels [13]. Substances reducing the fast inward sodium current (including tetrodotoxin) inhibit the disturbances of rhythm in the late stage of experimental myocardial infarction [13].

The writers have shown that ethacizine inhibits the fast inward current in myocardial fibers much more intensively than other quinidine-like drugs [3, 5]. This may perhaps explain why ethacizine increases the probability of ventricular fibrillation in acute coronary occlusion and why it has much greater antiarrhythmic activity than other quinidine-like drugs in the late stage of experimental myocardial infarction.

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