EFFECT OF THE DIETHYLAMINO ANALOG OF ETMOZINE AND CESIUM CHLORIDE ON THE IDIOVENTRICULAR RHYTHM IN DOGS IN THE LATE STAGE OF EXPERIMENTAL MYOCARDIAL INFARCTION

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The antiarrhythmic action of phenothiazone derivatives — etmozine and its diethylamino analog (DAA) — correlates with the effect of these drugs on the sodium current of the myocardial fibers: Compared with etmozine, its DAA inhibits the sodium current longer and more intensively, and that is probably why it abolishes arrhythmias in the late stage of experimental myocardial infarction for a longer period than etmozine [1, 2]. However, since arrhythmias in the late stage of myocardial infarction are due to automatic activity in the subendocardial Purkinje fibers located in the zone of ischemia [3, 6, 8, 11], it is not yet known to what degree the action of antiarrhythmic drugs and the arrhythmias themselves are connected with mechanisms determining normal automatic activity of the Purkinje fibers, i.e., with the pacemaker current I_{k2} [9]. To shed light on this problem the action of blockers of the I_{k2} current — cesium chloride [7] and etmozine DAA — on the idioventricular rhythm was compared in a control group of dogs and in dogs whose coronary artery was ligated 24 h before the main experiment.

EXPERIMENTAL METHOD

Experiments were carried out on mongrel dogs of both sexes weighing 10-20 kg under pentobarbital anesthesia (30-35 mg/kg, intravenously) and with artificial respiration. In the experiments of series I, under atrioventricular block conditions, the action of Cs^+ ions and etmozine DAA on normal automatic contractions of the ventricles was studied. For this purpose the chest of intact dogs was opened through the right third intercostal space and the pericardium incised. The endocardial local ECG of the right ventricle (VECG) and the ECG of the right atrium (AECG) were recorded by means of silver wire electrodes (0.2 mm diameter) with Teflon insulation, inserted into the myocardium by means of a surgical needle [10]. Electrical activity in the bundle of His (EBH) was recorded by a special catheter electrode (diameter 2 mm, interelectrode distance 10 mm), which was inserted into the right carotid artery and advanced as far as the base of the aorta [4]. The EBH, VECG, and AECG after amplification and filtration (30-250 Hz), and also the ECG (lead II) were led continuously to a monitor, and the necessary regions were recorded on photographic paper (winding speed 25-100 mm/sec) on a VR-12 recorder (Electronics for Medicine) (Fig. 1A). The atrioventricular block to conduction was created as follows. By means of a syringe with a curved fine needle a series of superficial injections (each 0.1 ml) of a 2% solution of lidocaine was given through the wall of the right atrium into the region of the posterior border of the atrial septum at the base of the aorta and of the tricupspid valve. When the lidocaine reached the atrioventricular node or bundle of His it blocked conduction, as was shown by disappearance of EBH, a sharp fall in the ventricular rhythm, and asynchronous contractions of the atria and ventricles (Fig. 1B). Conduction of excitation was restored 15-30 min later. On subsequent injection of 0.1-0.2 ml of 40% formalin solution into the region localized with lidocaine, an irreversible atrioventricular block of conduction developed. Solutions of CsCl

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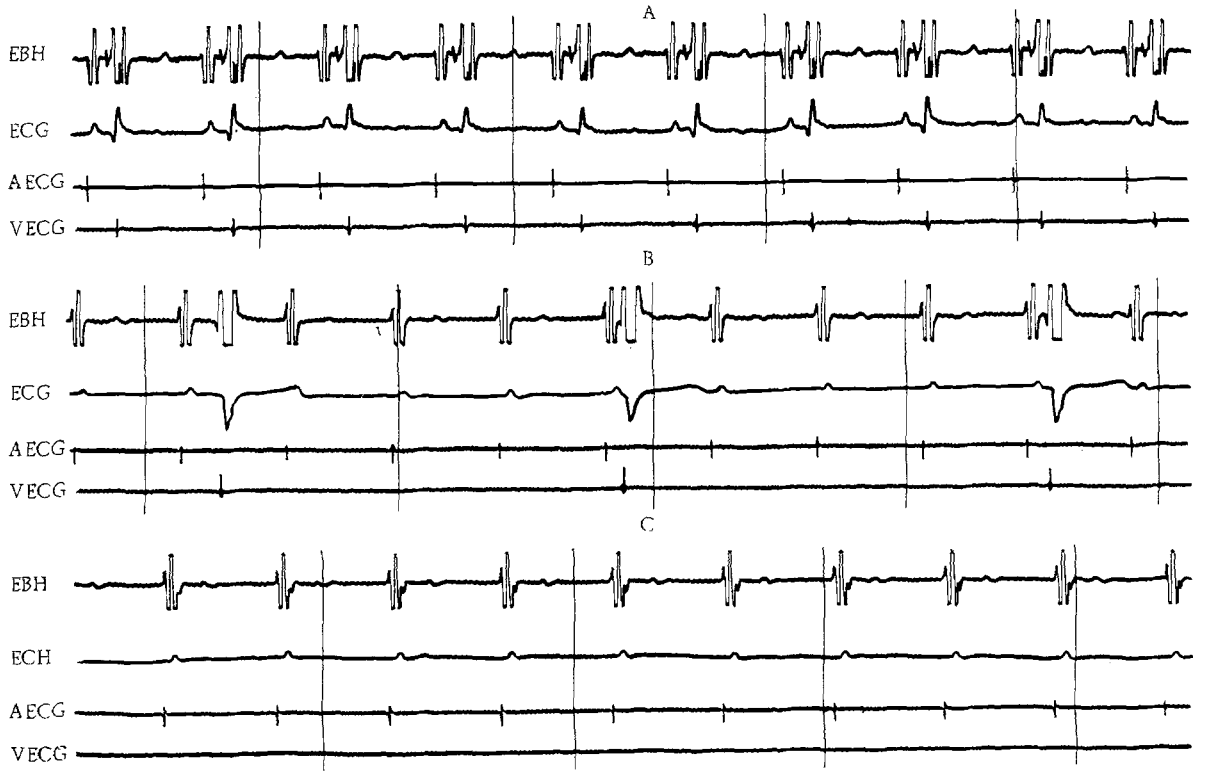

Fig. 1. Action of CsCl on idioventricular rhythm of intact dog. A) Control record; B) atrioventricular block; C) 1 min after injection of 20 mg/kg CsCl. AECG) Activation of atria; EBH) depolarization of bundle of His; VECG) activation of ventricles, amplitude of output signal clipped. Time marker 1 sec.

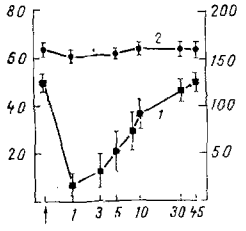

Fig. 2

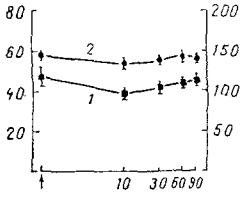

Fig. 3

Fig. 2. Action of CsCl (20 mg/kg) on idioventricular rhythm (1) and discharge frequency of sinus node (2) of intact dogs. Abscissa, time (in min); ordinate: left — idioventricular rhythm (beats/min), right — discharge frequency of sinus node (spikes/min). Arrow indicates end of injection of drug. Values shown are M ± m (n = 7).

Fig. 3. Action of etmozine DAA (1 mg/kg) on idioventricular rhythm (1) and discharge frequency of sinus node (2) of intact dogs. Legend as to Fig. 2 (n = 6).

(20 mg/kg) and etmozine DAA (1 mg/kg) were injected through a catheter into the femoral or jugular vein. In cases when injection of CsCl caused complete inhibition of ventricular rhythm, the heart was stimulated through needle electrodes at the base of the right ventricle with the frequency of the initial idioventricular rhythm (Fig. 1C). Every minute stimulation was interrupted for 40 sec. On the appearance of automatic contractions of the ventricles stimulation was stopped. The dogs used in the experiments of series II underwent two-stage occlusion of the left descending coronary artery by Harris' method [5] 24 h before the main experiment. The scheme of the experiments was basically the same as in series I. The difference was that during the period of creation of the atrioventricular block the heart

TABLE 1. Effect of Cesium Chloride (20 mg/kg) on Idioventricular Rhythm (beats/min) 24 h after Occlusion of Coronary Artery

Expt. No.	Control	Time after injection of CsCl, min	
		1	45
1	96	96	96
2	98	100	98
3	114	116	110
4	113	110	115
5	124	128	125
6	136	137	135
7	125	120	120
8	143	139	140
$M \pm m$	118,6±5,9	118,3±5,6	117,4±5,6

TABLE 2. Effects of Etomizine DAA (1 mg/kg) on Idioventricular Rhythm (beats/min) 24 h after Occlusion of Coronary Artery

Expt. No.	Control	Maximal fall of rhythm after injection of etmozine DAA	1 min after injection of 20 mg/kg CsCl against background of maximal fall of rhythm produced by etomize DAA	Freq. of ectopic ventricular excitation after injection of etmozine DAA	Time,* min	Duration,† min
1	92	41	0	0	10	82
2	98	29	0	0	11	88
3	100	77	76	77	14	89
4	110	58	23	0	10	26
5	117	50	20	0	10	38
6	100	39	0	0	10	55
7	143	110	112	110	4	40
8	142	27	0	0	6	22
$M \pm m$	111,5±7,2			23,4±15,6	9,4±1,1	55,0±9,8

*Time until maximal lowering of rhythm by etomozine DAA.
†Time of reduction of action of etmozine DAA on idioventricular rhythm by 50%.

was stimulated through electrodes in the right atrium at a frequency of 180-210/min in order to suppress ectopic ventricular excitation developing as a result of the myocardial infarct.

EXPERIMENTAL RESULTS

In five of the seven animals complete inhibition of normal automatic contractions of the ventricles was observed 1 min after injection of 20 mg/kg CsCl, and in another two dogs it was depressed by 34 and 42% below its initial level. Mean data for the action of CsCl are shown in Fig. 2. Clearly the effect of CsCl on automatic activity of the ventricles was most marked during the first few minutes after injection. The initial frequency of ventricular contractions was completely restored after 45 min. Meanwhile, CsCl caused virtually no change in the discharge frequency of the sinus node (the maximal decrease averaged 4.5%).

The action of etmozine DAA on normal automatic contractions of the ventricles developed much more slowly than the action of CsCl and reached a maximum 8-12 min after injection. As Fig. 3 shows, injection of 1 mg/kg etmozine DAA was followed by a small but not significant decrease in the frequency of the ventricular and sinus node rhythm (the maximal decrease averaged 19.4 and 7.8%, respectively).

Injection of 20 mg/kg CsCl had no effect on the idioventricular rhythm 24 h after occlusion of the coronary artery (Table 1) whereas injection of etmozine DAA in a dose of 1 mg/kg significantly depressed it (Table 2). The residual contractions of the ventricles after injection of etmozine DAA could be the result of ectopic foci of excitation in the zone of infarction or the result of normal automatic activity of the Purkinje fibers in the nonischemized myocardium. The second explanation was most probable in cases when the ventricular rhythm fell below 70 beats/min. Since CsCl inhibited normal automatic activity (Fig. 2) and did not affect the frequency of ventricular contractions in the late stage of myocardial infarction (Table 1), injection of CsCl against the background of the maximal lowering of the ventricular rhythm by etmozine DAA enabled the degree of inhibition of ectopic foci of excitation by the antiarrhythmic agent to be determined. As Table 2 shows, in four experiments injection of CsCl against the background of maximal lowering of the rhythm by etmozine DAA led to cardiac arrest, and in two other cases (Nos. 4 and 5) to marked slowing of the idioventricular rhythm. It can be concluded from these results that in these six experiments etmozine DAA completely suppressed foci of ectopic excitation in the zone of the infarct.

The results of this investigation showed that Cs^+ ions inhibit normal automatic activity but do not affect the frequency of ectopic ventricular excitation in the late stage of experimental myocardial infarction, whereas the antiarrhythmic agent etmozine DAA has only a very weak effect on normal automatic activity and significantly inhibits ectopic ventricular excitation. These findings indicate a difference in the ionic mechanisms responsible for normal automatic activity of the fibers of the conducting system and of those responsible for enhanced automatic activity, leading to the development of ectopic foci of excitation in the late stage of experimental myocardial infarction.

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