ANTIARRHYTHMIC AND ELECTROPHYSIOLOGICAL PROPERTIES OF ETMOZIN AND ITS DIETHYLAMINO ANALOG

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The effect of the antiarrhythmic drug etmozin and its diethylamino analog (DAA-etmozin) was compared in dogs with ventricular arrhythmias caused by ligation of the coronary artery. Both compounds were shown to abolish ventricular arrhythmias. However, DAA-etmozin had a more rapid and prolonged action. The electrophysiological properties of etmozin and DAA-etmozin were studied by the voltage clamp method on frog atrial trabeculae. Both compounds were shown to reduce the fast inward sodium current; DAA-etmozin had a stronger and more prolonged action.

KEY WORDS: antiarrhythmic activity; ectopic beats; etmozin and its diethylamino analog; fast inward sodium current.

It was shown previously that acyl derivatives of phenothiazine possess antiarrhythmic activity [1, 8]. One such compound, the Soviet preparation etmozin, has already been used clinically [2, 4]. The further study of the relationship between the chemical structure of 10-acylamino-derivatives of phenothiazine and their antiarrhythmic action led to the discovery of a compound which, according to several tests, has stronger antiarrhythmic activity than etmozin itself. The diethylamino analogs of etmozin (DAA-etmozin) were shown to be twice as active and to act for twice as long [5, 7]. In experiments on a model phospholipid membrane, DAA-etmozin showed twice the affinity of etmozin for the membrane [3].

The object of this investigation was to compare the effect of etmozin and its analog on ventricular disturbances of the cardiac rhythm in waking animals with experimental myocardial infarction and also to study the electrophysiological properties of these compounds.

EXPERIMENTAL METHOD

Experiments were carried out on dogs weighing 10-16 kg. The animals were anesthetized with pentobarbital sodium (35 mg/kg) intravenously. Under aseptic conditions the thorax was opened at the level of the fourth intercostal space. The pericardium was divided and the descending branch of the left coronary artery mobilized at the level of the apex of the left auricle. Two-stage ligation was carried out by the method described in [9]. The wound was closed in layers; a control recording of the ECG in standard lead II was carried out after 24 h. Substances for testing were injected intravenously in doses of 1-3 mg/kg (etmozin) and 0.5-1.5 mg/kg (DAA-etmozin). The numerical results were subjected to statistical analysis [6].

Ionic currents were recorded on isolated atrial trabeculae of Rana ridibunda. The preparations, 75-120 μ in diameter and 3-5 mm long, was placed in a perfusion chamber with a double sucrose gap [11]. To record the transmembrane potential (TMP) and apply current to the preparation, low-ohmic (under 5 kΩ) extracellular Ag-AgCl electrodes with agar bridges were used. To clamp the TMP and record ionic currents, the Dagan (USA) electronic circuit was used. The output voltage of the amplifier with negative feedback, clamping the TMP, was ± 90 V and the amplification factor 25,000. When the currents were recorded the assigned TMP was stabilized on the preparation for less than 100 μsec. The testing compartment of the chamber (200 μ wide) with a double sucrose gap was perfused with Ringer's solution of the following composition (in mM): NaCl 114,
Etmozin, in doses of between 1 and 3 mg/kg, given to waking dogs with ventricular arrhythmias, reduced the total number of cardiac contractions on average by 21%. As Fig. 1A shows, with an increase in the dose of etmozin the percentage of ectopic beats was reduced. A 100% effect (complete suppression of the ectopic rhythm) developed only after administration of etmozin in a dose of 2 mg/kg. The action of the compound began...