EFFECT OF ETHACIZINE (ETHMOZINE DIETHYLAMINE ANALOG) ON PHASE-DEPENDENT PARASYMPATHETIC EFFECTS ON THE HEART

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UDC 612.178.3.014.46:615.22:547.869.2

KEY WORDS: heart; parasympathetic innervation; ethacizine.

Ethmozine and ethacizine are phenothiazine derivatives which belong to a new group of highly active antiarrhythmic drugs developed at the Institute of Pharmacology, Academy of Medical Sciences of the USSR, and the All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR. According to the results of experimental and clinical investigations [2, 5, 10] ethacizine has the strongest antiarrhythmic activity and is often effective even in cases when other antiarrhythmics are ineffective. The antiarrhythmic action of ethacizine is based on its ability to inhibit activity of the fast sodium channels and, correspondingly, to reduce the rate of rise of action potentials of cardiomyocytes. There is also experimental evidence that ethacizine has a marked transient vagolytic action [6, 10]. The vagolytic properties of ethacizine were discovered in experiments on dogs in which the compound was injected intravenously and effects of vagus stimulation and of exogenous acetylcholine were tested. It was shown that ethacizine depresses both neurogenic parasympathetic effects and effects due to injection of acetylcholine. On this basis it was suggested that the vagolytic action of ethacizine resembles the action of atropine and is based on inhibition of mechanisms of interaction of acetylcholine with muscarinic acetylcholine receptors. Considering the prospects for widespread introduction of ethacizine into clinical practice and also the essential role of the parasympathetic innervation both in adaptive regulation of cardiac activity in pathology, it was decided to obtain more extensive and detailed information on the vagolytic properties of this drug. The chronotropic effects of vagus stimulation depend essentially on the phase of the cardiac cycle when the stimulation is applied [7-9]. This phase dependence is evidently determined by the kinetics of the isolation and diffusion of acetylcholine and its interaction with receptors, the rate of its removal from sites of contact with pacemaker structures, and also the temporal parameters of development of slow diastolic depolarization in pacemaker cells. The phase dependence may perhaps also play a part in the formation of the chronotropic reactions of the heart in the course of its reflex regulation in vivo.

The aim of this investigation was to study the action of ethacizine of parasympathetic phase-dependent chronotropic responses of the heart.

EXPERIMENTAL METHOD

Experiments were carried out on the frog (*Rana temporaria*) heart, perfused with Ringer's solution. The ECG and cardiac intervalogram were recorded. Stimulating electrodes were inserted intracranially at the site of emergence of the roots of the vagus nerve. Volleys of stimuli 100 msec in duration and with a frequency of 50-100 Hz in the volley were used. The triggering system enabled stimulation to be applied at different time intervals after the P wave. The interval between two stimulations was 1-1.5 min. The length of delay was increased by 100 msec in each successive stimulation, and it went through the whole cardiac cycle with the same "step." Initially the heart was perfused with Ringer's solution and the experiment was carried out after addition of ethacizine to the perfusion fluid. In the control, the effect was tested twice during perfusion without ethacizine. The magnitude of the effect was calculated as the ratio of the increase in duration of the cardiac cycle to the initial duration of the cycle. When the data were compared the following parameters of the effect were evaluated: 1) the maximal effect; 2) the latent period, or minimal time between stimulus and P wave at which changes in the duration of this cycle take place; 3) the time taken to reach the maximum — the interval between stimulus and P wave at which the

Department of Physiology of Man and Animals, Biological Faculty, M. V. Lomonosov Moscow University. (Presented by Academician of the Academy of Medical Sciences of the USSR I. P. Ashmarin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 105, No. 3, pp. 298-300, March, 1988. Original article submitted March 31, 1987.

0007-4888/88/0003-0347$12.50

TABLE 1. Effect of Ethacizine on Parameters of Phase-Dependent Chronotropic Parasympathetic Effect

Parameter	Ringer's solution		Ringer's solution	Ringer's solution + ethacizine (10^{-7} g/ml)	Ringer's solution	Ringer's solution + ethacizine ($5 \cdot 10^{-7}$ g/ml)	Ringer's solution	Ringer's solution + ethacizine (10^{-6} g/ml)
	test I	test II						
Magnitude of maximal effect, %	89±40	88±38	64±30	67±43	75±26	37±27*	96±48	17±14*
Latent period msec	1062±204	1104±203	1187±176	1166±186	952±160	1172±168*	1066±226	1309±259*
%	42±9	41±9	42±10	45±14	40±11	36±6*	50±7	40±12*
Time to reach maximum msec	1332±191	1436±237	1580±351	1649±372	1252±103	1600±186*	1431±340	1737±310*
%	23±15	21±15	23±15	23±15	20±13	7±8*	30±11	12±14*
Time of inhibitory effectiveness of vagal stimulus, msec	2950±878	3030±909	3600±1019	3560±1084	2992±502	2672±548	2734±560	2754±560
Duration of initial cycle, msec	1774±341	1890±366	2098±348	2200±310	1624±121	1820±197	2040±331	2160±125
Number of expts.	10	10	9	9	5	5	7	7

Legend. Asterisk indicates significant change in parameter under the influence of ethacizine when compared with corresponding values in the same experiments but during perfusion with Ringer's solution without ethacizine.

maximal effect was observed; 4) the duration of inhibitory effectiveness of the vagal stimulus — maximal time from stimulus to P wave at which the effect amounted to about 10% of maximal. The latent period and time taken to reach the maximum were calculated in absolute units (milliseconds) and as a percentage of the initial duration of the cycle. The significance of differences was estimated by nonparametric tests, and a rank test for paired samples was used [1].

A fuller description of the methods used to calculate and analyze the data will be found in [3].

EXPERIMENTAL RESULTS

Under the experimental conditions used a vagolytic action of ethacizine was discovered in concentrations of $5 \cdot 10^{-7}$ and 10^{-6} g/ml (a concentration of 10^{-7} was ineffective). The experimental results are summarized in Table 1.

It will be clear from Table 1 that under the influence of ethacizine in a concentration of 10^{-6} and $5 \cdot 10^{-7}$ g/ml the maximal effect was significantly reduced, the time to reach the maximum was increased and shifted toward an earlier phase of the cardiac cycle, and the latent period also was increased. No significant changes were found in the time of inhibitory effectiveness of the vagal stimulus. In most experiments there was a tendency for slowing of the rhythm to take place with time, but this slowing was equally marked against the background of perfusion with Ringer's solution alone and with ethacizine.

Previous investigations [4] showed that ethacizine has an effect in a concentration of 10^{-5} g/ml on the slow inward Na-Ca current, so that it may have an action on the cardiac rhythm. However, in the concentrations which we used, no significant changes were found in the cardiac rhythm.

Changes in the character of phase-dependent vagal effects caused by ethacizine were similar in their general features to those observed previously in response to reduction of the parameters of vagal stimulation [3]. In both cases, evidently, these changes are due to a final common cause — a decrease in the degree of binding of acetylcholine with receptors and a corresponding decrease in the hyperpolarization shift on the pacemaker cell membrane. However, whereas with a change in the parameters of stimulation this is connected with a decrease in the neurogenic release of acetylcholine, considering the inhibitory action of ethacizine on the effect of exogenous acetylcholine, this suggests that during its action some acetylcholine receptors are blocked, and this leads to a similar after-effect.

The absence of any appreciable influences on the time of inhibitory effectiveness of the vagal stimulus evidently indicates that the hydrolysis of acetylcholine and the length of its contact with the acetylcholine receptors are not significantly changed by ethacizine.

The authors are grateful to colleagues in the Laboratory of Electrophysiology of the Heart, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, for providing the ethacizine and for giving scientific advice.

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