ETHMOZINE AND ETHACIZINE - NEW ANTIARRHYTHMIC DRUGS WITH DEFIBRILLATING PROPERTIES

Dalia Varon, Moshe Rechavi, Mordechai Erez, Gabriella Goldberg, Mordechai Manoach and Natalia V. Kaverina*

Department of Physiology and Pharmacology, Tel Aviv University School of Medicine, Tel-Aviv, Israel
**Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow, Russia*

ABSTRACT

Ventricular fibrillation (VF) is a life-threatening arrhythmia that leads to death unless electrical defibrillation is applied in time. Recent publications indicate that VF can be either sustained (SVF), requiring electrical defibrillation, or transient (TVF), reverting spontaneously into sinus rhythm. Since VF cannot be totally prevented by drugs, a new antiarrhythmic therapeutic approach has been proposed: drug-induced enhancement of the ability of the heart to defibrillate by itself.

In this study we examined the defibrillating potency of two antiarrhythmic phenothiazines, ethmozine (ETM) and ethacizine (ETA), as well as their effects on catecholamine uptake and on the electrophysiological properties of the myocardial cell membrane.

The antiarrhythmic-defibrillatory activity was examined in cats; the inhibitory effect on [^{3}H]-norepinephrine (NE) uptake was examined in rat brain synaptosomes, and the electrophysiological membrane effects were examined by microelectrode recordings in perfused strips of heart ventricle from guinea-pigs.

The results indicate that: 1. ETA exhibits similar but stronger antiarrhythmic-defibrillating and NE reuptake inhibitory effects than ETM; 2. ETA at 10^{-6} M decreases ventricular conduction time and increases V_{max} while ETM at this concentration does not change them; 3. The defibrillating ability of the drugs can be related to their inhibitory potency on NE reuptake.

Accepted 8 August 1993

We suggest that the risk of sympathomimetic arrhythmogenicity is prevented by the previously described, membrane stabilizing Class 1 antiarrhythmic properties of these drugs.

KEY WORDS

ethmozine, ethacizine, phenothiazines, antiarrhythmic drugs, antifibrillatory drugs, spontaneous ventricular defibrillation

INTRODUCTION

Ventricular fibrillation (VF) is one of the major causes of sudden death in humans. Once VF appears, the heart ceases to function as a pump, blood circulation terminates, and death is imminent, unless electrical defibrillation is applied within a few minutes. Following the assumption that electrical defibrillation is the only method that can terminate VF in humans, the currently used antiarrhythmic drugs are aimed at preventing initiation of VF by decreasing the incidence of ventricular premature beats and/or ventricular arrhythmias which can lead to VF. However, from clinical and theoretical considerations, it seems now that since different mechanisms can be involved in the initiation of VF /1/, it is almost impossible with drugs to totally prevent the appearance of ventricular arrhythmias and, thereby, VF. Because of these limitations, a new antifibrillatory therapeutic approach has been proposed to help the heart to defibrillate by itself /2/.

Self-terminating VF (transient VF - TVF) has been observed in various small mammals such as rats, guinea-pigs and rabbits /3/. The ability of the hearts of small mammals to defibrillate has been correlated with their ventricular muscle mass /4/. It was suggested that VF in small hearts tends to terminate spontaneously since they do not have the minimal number of cells required for the maintenance of the fibrillating process /4,5/. Following this theory, it has been suggested that the human heart, with a large muscle mass, cannot defibrillate spontaneously. However, recent publications indicate that VF can terminate spontaneously in relatively large mammalian hearts (puppies) /6/ and even in humans /7-10/, while the small hearts of birds (pigeons and hens) /6/ exhibit sustained ventricular fibrillation (SVF). In addition, it has been found that certain drugs, such as

bretylium tosylate and its derivative clofilium /11,12/, several tricyclic antidepressants and phenothiazines /13-16/, enhance the ability of the heart to defibrillate spontaneously. These facts led us to investigate the physiological differences between SVF and TVF as well as the mechanisms involved.

The results, obtained in animals of both sexes and of various species and ages /6,13,17/, indicate that: a) the ability to defibrillate spontaneously is a normal feature in young mammals; b) this ability decreases with age; c) the age span in which TVF appears varies between species; d) there is no significant difference between the cardiac muscle mass of mammals that exhibit TVF and those that respond with SVF; and e) in TVF the cardiac cells of both ventricles exhibit a relatively slow rate and well synchronized fibrillating activity, while in SVF the ventricular cells fibrillate at a higher rate and in a less synchronized manner.

On the basis of these results we hypothesize that TVF requires high intercellular synchronization /6,18/. A similar hypothesis has also been proposed by Kobrin *et al.* /19/. In young mammals this intermyocardial cell synchronization is obtained by high sympathetic and low parasympathetic cardiac activity at the time of VF, caused by sympathetic predominance of the heart autoregulation /6,14-17/. This hypothesis has been supported by the fact that the above-mentioned drugs reported to enhance the occurrence of self defibrillation /11-16/ share the ability to increase the local cardiac level of cathecholamines, during VF, by inhibition of catecholamine reuptake into the adrenergic nerve terminals and/or inhibition of MAO activity /20-22/. The role of catecholamines in self-defibrillation has been emphasized by the fact that various compounds that elevate catecholamine level (like amphetamine) transform SVF into TVF /14,15,17,23/, while beta-adrenergic blockers (propranolol and pindolol), administered in mammals which exhibited TVF before their administration, transformed the type of VF into SVF /15,17/.

In this study we examined the electrophysiological and defibrillating activity of two antiarrhythmic phenothiazies: ethmozine (ETM) (moricizine) /24/ and its new diethylamine analogue - ethacizine (ETA) /25,26/, as well as their effect on catecholamine reuptake.

MATERIALS AND METHODS

The drugs used were received from the department of Prof. N.V.

Kaverina, Russian Academy of Medical Sciences, Moscow, Russia. The drugs were prepared from powder and dissolved in saline.

Antiarrhythmic-defibrillatory activity

The antiarrhythmic-defibrillatory activity of ETM and ETA was examined on 10 cats per drug, of both sexes. The cats were anesthetized with 15-25 mg/kg i.v. sodium pentobarbital. The hearts were exposed through a midline thoracotomy and a room air respirator was applied through a tracheal cannula. L_{II} ECG and intra-arterial blood pressure were recorded on a Grass Polygraph.

The fibrillating stimuli (train of rectangular pulses: 2-15 V, 100 pps, and duration of 0.1-1.0 msec, for a period of 0.5 sec) were delivered through 2 silver needle electrodes attached to the pericardium on the left ventricle. The fibrillating stimuli were 1.5-2 times the strength of the fibrillating threshold.

Animals were designated as having SVF if VF failed to terminate spontaneously within 90 sec and required electrical defibrillation. Animals that exhibited 2-5 consecutive episodes of VF of short (20-60 sec) duration were designated as having TVF.

[^{3}H]-Norepinephrine uptake

The uptake of [^{3}H]-norepinephrine (NE) into synaptosomes was measured essentially as described by Coyler and Snyder /27/. Forebrain (whole brain minus brain stem and cerebellum) of adult male Charles-River rats was homogenized in 10 vol of ice-cold 0.32 M sucrose in a Potter-Elvehjem homogenizer (10 strokes), using a teflon pestle. The homogenate was centrifuged at 1000 *g* for 10 min and the resulting supernatant containing the synaptosomal membranes was used for the uptake study. A standard assay contained: 50 µl homogenate, 50 µl tritiated NE (3×10^{-8} M, 11.4 Ci/mmole) and 850 µl modified Krebs-Ringer-phosphate buffer (119 mM NaCl, 3.9 mM KCl, 0.65 mM $MgSO_4$, 0.51 mM $CaCl_2$ and 0.19 mM sodium phosphate buffer, pH 7.4 in a total volume of 1.0 ml). The buffer solution was equilibrated with 95% O_2 - 5% CO_2 for 10 min prior to use. The buffer also contained glucose (2 mg/ml), ascorbic acid (0.2 mg/ml), EDTA (0.06 mg/ml) and pargyline (10^{-4} M). The tubes were preincubated at 37°C for 10 min, at which time the radioactive compounds were added. After incubating at 37°C for 4.0 min the reaction was stopped by adding desmethyl-imipramine (1×10^{-5} M) and rapidly cooling the tubes on ice. Specific uptake was measured in

the presence of 1 x 10^{-5} M desmethyl-imipramine. The incubate was diluted in 5 ml ice-cold buffer and filtered under vacuum through Whatman GF/C filters. Filters were washed 3 times with 5 ml ice-cold buffer and counted in 4 ml Optifluor in a Packard 300C scintillation counter. The inhibitory effect of ETM and ETA was assessed by replacing 50 µl of the buffer in the incubation assay by 50 µl of the tested drug (10^{-7} M - 10^{-4} M).

Microelectrode recording in guinea-pig ventricular myocytes

Ten adult guinea-pigs of either sex (200 - 300 g) were stunned by a blow to the neck and rapidly exsanguinated. The heart was removed and the left ventricle dissected free in oxygenated Tyrode's solution at room temperature. The excised ventricle was placed in a 10 ml tissue chamber lined with Sylgard. The bath was perfused at a constant rate of 3-5 ml/min and gassed with 95% O_2 and 5% CO_2. The temperature of the perfusate was maintained at 33 ± 0.5°C.

Transmembrane potentials were recorded from left ventricular myocytes, according to Bigger *et al.* /28/, through glass capillary microelectrodes having a resistance of 10-15 MOhms. The microelectrodes were filled with 3M KCl and were attached to a silver wire leading to a home-made amplifier having high input impedance. The records of transmembrane potential and the dV/dt of their phase 0 were displayed on a dual beam storage Tektronix cathode-ray oscilloscope and photographed with a polaroid camera.

Driving stimuli (2 pps, 10 V and duration of 0.1 msec) were delivered to the left ventricular strip by means of a bipolar silver electrode using a Grass model S88 stimulator.

RESULTS

Defibrillating effect in open chest anesthetized cats

Intravenous administration of either ETM or ETA elevated the fibrillating threshold and exhibited a significant defibrillating effect. VF that was induced after their administration either by electrical stimuli or by coronary occlusion and reperfusion terminated spontaneously within 2-60 seconds after its initiation (Fig. 1, Table 1). It was found that the defibrillating effect of ethacizine was more prominent than that of ethmozine at equal dosage levels. It was also found that the effectiveness and duration of this cardioprotective

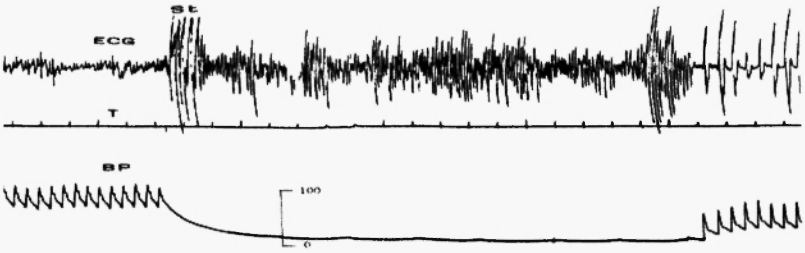

Fig. 1: Self-terminating electrically induced ventricular fibrillation (TVF) in a cat treated with ethacizine (1 mg/kg). From top to bottom: L_{II} ECG, time (T) in sec, blood pressure (BP). St - electrical stimuli.

TABLE 1

Compound	Relative (%) defibrillating activity TVF/VF*	ED_{50} mg/kg bolus	infusion	IC_{50} (μ) for NE uptake#
Ethacizine	75 - 80	1	3	1.7×10^{-5}
Ethmozine	55 - 60	3	7	4×10^{-5}

* TVF/VF - Number of TVF out of total number of VF, obtained in cats treated by 3 mg/kg in bolus.

\# Measured in brain synaptosomes

effect (the period of time during which VF terminated spontaneously) was dose-dependent. The minimal effective doses of i.v. injection (bolus) needed for obtaining a protective duration of 10-20 min were 1 mg/kg for ETA and 3 mg/kg for ETM. The minimal effective doses of slow i.v. infusion needed for obtaining protective duration of 4-6 h were 3 and 7 mg/kg respectively (Table 1).

Ethmozine and ethacizine have to be injected slowly, since fast i.v. administration can cause side effects /29/, including partial AV block, changes in cardiac vector. These side effects terminate within a few minutes after termination of drug administration.

Electrically induced VF in animals treated with an overdose of either ETM or ETA either transformed into sinus rhythm, through transient ventricular tachicardia (TVT) (Fig. 2), or exhibited sustained ventricular tachycardia.

Administration of a beta-blocker (propranolol) following ETM or ETA treatment antagonized their defibrillating effect in a competitive manner.

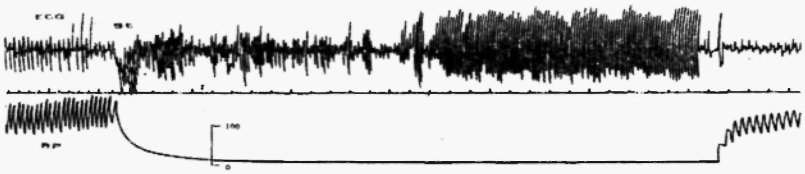

Fig. 2: Self-terminating electrically induced ventricular fibrillation in a cat treated by overdose of ethacizine (3 mg/kg) reverting to sinus rhythm through transient ventricular tachycardia.

Inhibitory effect on catecholamine uptake in rat brain synaptosomes

Examination of the two compounds showed that they share the ability to inhibit NE uptake in the rat brain synaptosomal preparation *in vitro*, and that ethacizine exhibited a stronger effect than ethmozine (Table 1).

Electrophysiological effects in guinea-pig ventricular myocytes

Administration of ETA (10^{-6} M) increased V_{max} by 21% (after 5 min perfusion) and decreased conduction time in guinea-pig ventricular myocytes (Fig. 3), while administration of ETM at the same concentration had no effect. Administration of either ETA or ETM at the same concentration of 10^{-6} M in preparations pretreated with beta-blocker showed a 19% decrease in V_{max} after 5 min perfusion.

DISCUSSION

ETM and ETA are structurally closely related phenothiazine derivatives synthesized by Prof. Kaverina and her colleagues in the Russian Academy of Medical Sciences /24-26/. They have both been reported to be potent antiarrhythmic and antifibrillating drugs in animals and in humans /29-36/, ETA exhibiting a similar but more potent antiarrhythmic effect with a longer duration of action than ETM /25,34,37,38/.

Ethmozine and ethacizine, like other phenothiazines and tricyclic antidepressants, have been grouped as Class I antiarrhythmics /38-42/, although Bigger /41/ notes that "there is some confusion with the classification of moricizine" in the Vaughan Williams Class I subgroups /43/.

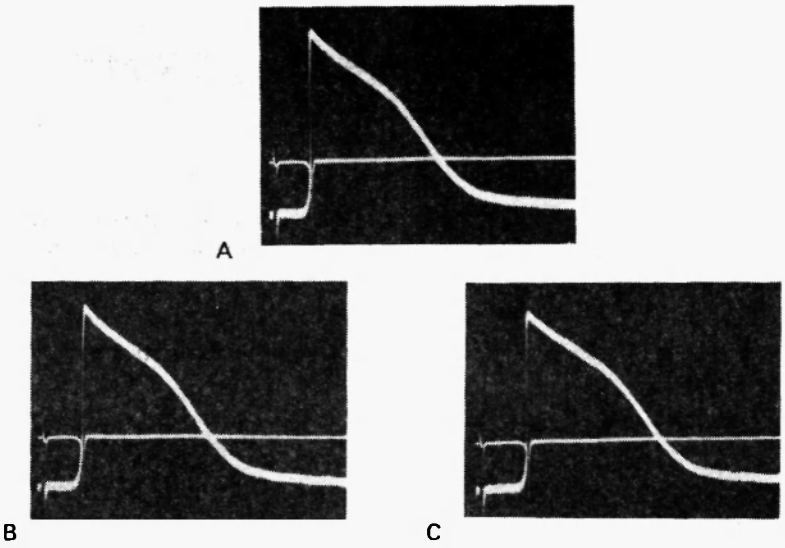

Fig. 3: Microelectrode recordings of action potential (AP) in guinea-pig myocardial cell (lower trace) and V_{max} of phase 0. A-control; B-3 min of infusion of ethacizine 10^{-6} M; C-5 min of perfusion. Calibration: horizontal - 20 msec; vertical - for V_{max} 100 V/sec and for AP 20 mV.

It has been reported that through their direct Class I antiarrhythmic effects they both produce concentration - frequency dependent reduction of the fast Na^+ inflow current /42,44/, whereas Makielevsky *et al.* /45/ suggest that the effect of ETA on the Na^+ inward current differs from that of ETM. According to their reducing effect on the Na^+ inward current, they both produce a concentration dependent, moderate reduction in action potential upstroke velocity (V_{max}), in action potential amplitude, in action potential duration, in the duration of an effective refractory period, and in the overshoot of the slow response action potential, as well as a slight decrease in conduction velocity, in excitability of cardiac fibers and in their membrane responsiveness /41,42,44,45/, while resting potential remains unchanged /46/.

Although ETM and ETA are closely related compounds, several of their effects have been reported to be diametrically opposed. For example, ETM has been reported to increase the slow Ca^{++} inward current /46/ while Starmer *et al.* /47/ reported that ETA decreases the slow Ca^{++} inward current in a frequency-voltage-concentration manner. Similar reports about different actions of ETM and ETA exist

also with regard to the inotropic effects of ETM (positive) and ETA (negative) /48/, as well as on their effect on SA node and AV junction /49/.

These "direct" effects and especially the fact that ETM and ETA decrease the spontaneous sympathetic discharge /50/ can explain the antiarrhythmic properties of these drugs.

The results of our present study on CNS synaptosomes indicate that ETM and ETA exhibit an inhibitory effect on NE uptake. Similar reuptake inhibitory properties are exhibited by many phenothiazines and tricyclic antidepressants /51,52/. Due to their ability to inhibit catecholamine reuptake and their vagolytic property /53/, ETM and ETA share certain indirect sympathomimetic effects, i.e., they increase V_{max}, increase intercellular conductance and electrotonic space constant, and thereby increase conduction velocity and intercellular coupling and synchronization /23,54,55/.

Since ETM and ETA exhibit strong defibrillating ability, which is not found in many Class I antiarrhythmics, we suggest that their defibrillating potency results from their inhibitory effect on catecholamine reuptake /23/, in addition to their cholinolytic one /56/. This assumption fits the finding that ETA, which is more potent in inhibition of catecholamine reuptake, exhibits more potent defibrillating ability. This hypothesis is also strengthened by the fact that administration of a beta-adrenoceptor blocker (propranolol) in animals pretreated with ETM or ETA antagonizes their defibrillating effect.

Taking into consideration these direct and indirect effects, it seems that ETM and ETA share with other phenothiazines and tricyclic antidepressants properties known to affect in opposite directions the action potential configuration and its intercellular propagation. This is probably the reason which led Bigger /41/ to describe ETM as having a unique electrophysiologic profile.

Since ETM and ETA share two opposite effects, what is their net effect *in vivo*?

We suggest that the effect of ETM and ETA depends on the physiological situation. In all cases, except VF, the dominant effect is that of a Class I antiarrhythmic. According to these Class I properties, and especially due to their ability to decrease sympathetic discharge even in the case of myocardial infarction /50/, they both serve as potent antiarrhythmic drugs. For these reasons, they have been described as drugs which at therapeutic doses, do not cause severe side effects and do not elevate the normal ventricular rate /57/.

On the other hand, during VF sympathetic activity is enhanced and the catecholamine level is thereby increased, mainly due to the inhibitory effect of the drugs on catecholamine reuptake. Due to the increase in cardiac catecholamine level, intracellular resistance decreases and intercellular coupling increases. With ETA V_{max} and conduction velocity increase. These indirect effects lead to an enhancement of intercellular synchronization and help the heart to defibrillate by itself.

CONCLUSION

It was found that both ETM and ETA have a potent defibrillating effect, in addition to their antiarrhythmic and antifibrillating ones. This defibrillating effect can be related to their inhibitory effect on the catecholamine reuptake demonstrated in this study, while the risk of sympathomimetic arrhythmogenicity is prevented by the membrane stabilizing Class I antiarrhythmic property of the drugs. We suggest that during clinical and experimental conditions, other than VF, ETM and especially ETA serve as antiarrhythmic drugs, while during VF they serve as defibrillating drugs, enhancing the ability of the heart to defibrillate by itself. These complementary cardio-protective properties might serve as a lead for the development of new more effective antiarrhythmic-defibrillating drugs.

REFERENCES

1. Working group on arrhythmias, European Society of Cardiology. The Sicilian Gambit: A new approach to the classification of antiarrhythmic drugs based on their action on arrhythmogenic mechanisms. Circulation 1991; 84: 1831-1851.
2. Manoach M, Varon D, Neuman M, Erez M. Editorial. A new group of defibrillatory drugs in the classification of antiarrhythmic agents. Int J Cardiol 1988; 21: 211-217.
3. Wigers CJ. Studies of ventricular fibrillation caused by electrical shock. Am Heart J 1929; 5: 351-365.
4. Zipes DP, Fisher J, King RM, Nicoll AB, Jolly WW. Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium. Am J Cardiol 1975; 36: 37-44.
5. West TC, Landa JF. Minimal mass required for induction of sustained arrhythmias in isolated atrial segments. Am J Physiol 1962; 202: 232-236.
6. Manoach M, Varon D, Neuman M, Netz H. Spontaneous termination and initiation of ventricular fibrillation as a function of heart size, age, autonomic

autoregulation and drugs: A comparative study on different species of different age. Heart & Vessels 1987; 2(suppl): 56-68.

7. Schwartz SP, Orloff J, Fox C. Transient ventricular fibrillation. Am Heart J 1949; 37: 21-35.
8. Goble AJ. Paroxysmal ventricular fibrillation with spontaneous reversion to sinus rhythm. Br Heart J 1965; 27: 62-68.
9. Josephson ME, Spielman SR, Greenspan AM, Horowitz LN. Mechanism of ventricular fibrillation in man. Am J Cardiol 1979; 44: 623-631.
10. Clayto R, Higham D, Murray A, Camtpell R. Self terminating ventricular fibrillation. J Am Coll Cardiol 1992; 19: 265A (abstract).
11. Bacaner M. Bretylium tosylate for suppression of induced ventricular fibrillation. Am J Cardiol 1966; 17: 528-534.
12. Steinberg MI, Molley BB. Clofilium - A new antifibrillatory agent that selectively increases refractoriness. Life Sci 1979; 25: 1397-1406.
13. Manoach M, Kauli N, Netz H, Beker B, Assael M. Dibenzepin as an antifibrillatory agent for spontaneous terminating electrically induced ventricular fibrillation. Israel J Med Sci 1979; 15: 443-447.
14. Manoach M, Varon D, Neuman M, Erez M. Minireview: The cardio-protective features of tricyclic antidepressants. Gen Pharmac 1988; 20: 269-275.
15. Manoach M, Beker B, Erez M, Varon D, Netz H. Spontaneous termination of electrically induced ventricular fibrillation. In: Macfarlane PW, ed, Progress in Electrocardiology. England: Pitman Med Pub, 1979; 361-365.
16. Wosner D. A Study of Tricyclic Antidepressnats, Phenothiazines and Ca^{++} Blockers, Comparing their Effects on Spontaneous Termination of VF and Reduction of the Ischemic Area Following MI in Feline. M.Sc.Thesis. Tel-Aviv Univ Med School, Israel, 1990.
17. Manoach M, Netz H, Erez M, Weinstock M. Ventricular self defibrillation in mammals: age and drug dependence. Age & Ageing 1980; 9: 112-116.
18. Manoach M, Netz H, Beker B, Kauli N. Vector-cardiographical discrimination between sustained and transient ventricular fibrillation. In: dePadua F, Macfarlane PW, eds, New Frontiers of Electrocardiology. England: Research Studies Press, J Wiley & Sons, 1981; 139-143.
19. Kobrin VI, Kositsky GI, Haspecova NB. Electrophysiology of defibrillation. In: Szekeres L, Papp JG, Takate I, eds, Sudden cardiac death. Budapest: Akademia Kiado, Publishing house of Hungarian Academy of Sci, 1982; 196-172.
20. Collingham BA. The effect of imipramine and related compounds on the uptake of noradrenaline into sympathetic nerve endings. In: Garattini S, Dukes M, eds, Antidepressant Drugs. Milan: Excerpta Medica Fondation, 1967; 35-43.
21. Hertting G, Axelrod J, Patrick RW. Action of bretylium and guanethidine on the uptake and release of ^{3}H-noradrenalin. Br J Pharmacol 1962; 18: 161-166.
22. Giachetti A, Shore PA. Monoamine oxidase inhibition in the adrenergic neuron by bretylium, debrisoquin and other adrenergic neuronal blocking agents. Biochem Pharmacol 1967; 16: 237-238.
23. Manoach M, Erez M, Wozner D, Varon D. Ventricular defibrillating properties of catecholamine uptake inhibitors. Life Sci 1992; 51: 159-164.
24. Kaverina NV, Senova ZP, Mitrofanov VS et al. Pharmacology of ethmozin - a

new antiarrhythmic drug. Phamacol Toxicol 1972; 35: 182-185.
25. Kaverina NV, Lyskovtsev VV, Senova ZP, Girorieva EK. Ethacizine: pharmacologic properties and prospect for clinical application. Kardiologia 1984; 24: 52-57.
26. Kaverina NV, Skoldinov AP, Senova ZP, Vikhljajer I. Pharmacology of ethacizine. Famakol Toksikol 1985; 5: 43-49.
27. Coyle JT, Snyder SH. Catecholamine uptake by synaptosomes in homogenates of rat brain. J Pharmacol Exp Ther 1969; 170: 221-231.
28. Bigger JJ Jr, Bassett AL, Hoffman BF. Electrophysiological effect of diphenylhyldantoin on canine Purkinje fibers. Circ Res 1968; 22: 222-236.
29. Lazutin VK, Simonov VI, Glezer MG, Fonsova EA, Khapilin PA. Clinical effectiveness of ethacizine in various methods of intravenous administration. Kardiologia 1988; 28: 52-55.
30. Lukoshiavichiute AI, Gedrimene DA. Clinical effectiveness of ethacizine in the treatment of supraventricular paroxysmal tachycardia. Ter Arkh 1988; 60: 41-46.
31. Aniunkhovskii EP, Vegkh A, Rozenshtraukh LV, Szekeres L. Effect of etmozin and ethacizin on local microcardiac blood flow and the fibrillation threshold of the heart. Kardiologia 1984; 24: 58-61.
32. Kaverina NV, Sehova ZP, Vikhljajer I. Antiarrhythmic properties of etmozin. Farmakol Toksikol 1970; 33: 693-697.
33. Ruffy R, Rozenshtraukh LV. Electrophysiological effects of etmozin on canine myocardium. Cardiovasc Res 1979; 13: 354-368.
34. Smetnev AS, Shugushev KhKh, Rozenshtraukh LV. Clinical electrophysiologic and antiarrhythmic efficacy of moricizine HCl. Am J Cardiol 1987; 60: 40F-44F.
35. Rozenshtraukh LV, Aniukhovskii EP, Beloshapka GG. Effect of the dielthylamine analog of etmozin and cesium chloride on the idioventricular rhythm in dogs in the late stage of experimental myocardial infarction. Bull Exp Biol Med 1981; 91: 453-456.
36. Kukes VG, Smetnev AS, Ponomerenko EL, Burian EF, Storodubtsev AK. A new Soviet drug ethacizine in the treatment of ventricular rhythm disorders. Kardiologia 1983; 23: 45-47.
37. Smetnev AS, Pnonmarenko EL, Koltunova MI, Shugushev KhKh. Comperative study of the effectiveness of etmozine, ethacizine and Ritmilen in patients with ventricular rhythm disorders. Kardiologia 1987; 27: 24-26.
38. Kaverina NV, Sokolov SF. Pharmacology and clinical use of a new group of antiarrhythmic drugs: derivatives of tricyclic nitrogen containing systems. Pharmacol Res 1992; 25: 217-225.
39. Arita M, Surawicz B. Electrophysiologic effect of phenothiazines on canine cardiac fibers. J Pharmacol Exp Ther 1973; 184: 619-630.
40. Shugushev KhKh, Rozenshtraukh LL, Portnoi VF, Dvotsin GF, Iusmanova AV. Electrophysiological study of the cardiotraphic action of phenothiazine derivative antiarrhythmic preparations. Kardiologia 1986; 26: 36-40.
41. Bigger JT Jr. Cardiac electrophysiologic effects of Moricine Hydrochloride. Am J Cardiol 1990; 65: 15D-20D.
42. Zipes DP, Troup PJ. New antiarrhythmic agents: Amiodarone, aprindine, disopiramide, etmozin, mexiletine, tocainide, verapamil. Am J Cardiol 1978; 41: 1005-1024.

43. Vaughan Williams, E.M. Classification of Antiaarhythmic Drugs. In: Sandoe E, Flansted Jansen E, Olsen KH, eds, Symposium on Cardiac Arrhythmias; Sudertalje, Sweden: AB Astra, 1970; 449-472.
44. Rozenshtraukh LV, Anuchovski EP, Beloshapko GG, Dremin SA. Decrease in the fast sodium inflow current, a possible reason for the anti-arrhythmic action of etmozin and mexityl in the late stage of experimental myocardial infarction. Kardiologia 1980; 20: 19-22.
45. Makielevsky aC, Nesterenko VV, Nelson WL, Undrovinas AI, Starmer CF. State dependence of ethacizine and etmozin block of sodium current in voltage clamped and internally perfused cardiac Purkinje cells. J Parmacol Exp Ther 1990; 253: 1110-1117.
46. Rosenshtraukh LV, Anyukhovsky EP, Nesterenko VV, Undrovinas AI, Shugushev KKh, Portnoy VF, Burnashev NA. Electrophysiologic aspects of moricizine HCl. Am J Cardiol 1987; 60: 27F-34F.
47. Starmer CF, Undrovinas AI, Scamps F. Vassort G, Nesterenko VV, Rosenshtraukh LV. Ethacizine blockade of calcium channels: A test of the guarder receptor hypothesis. Am J Physiol 1989; 257: (5pt2) H1693-1704.
48. Ulthaler F, Rosenshtraukh LV, Walker AA, Hageman GR. Differential inotropic action of etmozin and ethacizine (diethylaminic analogue of etmozin). Am Heart J 1986; 111: 462-465.
49. Ulthaler F, Rosenshtraukh LV, Hageman GR, Anjukhovsky EP, James TN. Different modulation of autonomic activity by etmozin and ethacizine on the canine sinus node and atrioventricular junction. J Am Coll Cardiol 1986; 8: 86A-94A.
50. Hageman GR, Neely BH, Urthaler F, Rosenshtraukh LV. Effects of the dielthylamino analog of ethmozin (ethacizin) upon sympathetic and parasympathetic efferent activity tot he canien heart. J Pharmacol Exp Ther 1986; 236: 75-79.
51. Waldmeier PC, Baumann P, Green grass PM, Maitre L. Effect of clomipramine and other tricyclic antidepressants on biogenic amine Uptake and turnover. Postgrad Med J 1976; 52: Suppl. 3: 33-39.
52. Waldmeier PC, Baumann PA, Wilhelm M, Bernasconi R, Maiter L. Selective inhibitor of noradrenaline and serotonin uptake by C49802-B-Ba and CGP 6085A. Eur J Pharmacol 1977; 46: 387-391.
53. Savelijeva MV, Rathez EI, Baldenko GH, Kaverina NV. Differences in the efficiency of their interaction with membrane receptors of the dialkylaminoalkyl and dialkylaminoacyl derivatives of phenothiazine. Biull Eksp Biol Med 1990; 109: 266-268.
54. Manoach M, Erez M, Varon D. Editorial review. Properties required for self ventricular fibrillation: Influence of age and drugs. Cardiol in the Elderly. 1993; in press.
55. Manoach M, Ben-Basat M. The structural functional basis of spontaneous ventricular defibrillation. Int J Cardiol 1990; 26: 129-136.
56. Rather EI, Baldenkov GN, Grigorian GY, Rosenshtraukh LV, Tkachuk VA. Moricizine and ethacizine effects on membrane receptors. Arzneimittel Forschung 1989; 39: 766-769.
57. Shugushev KhKh, Malakhev Vi, Shestakova NV. First result of the clinical use of ethacizine in patients with paroxysmal atrial fibrillation. Ter Arch 1986; 53: 49-52.