Comparative Study of Antiarrhythmic Effects of Methacizin and Its Components under Conditions of Neurogenic Atrial Fibrillation

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Antifibrillatory effect of methacizin under conditions of neurogenic atrial fibrillation in cats was due to its vagolytic rather than cardiotropic activity. The immediate antifibrillatory effect of methacizin surpassed that of its components (ethacizin and ethmozin). However, 30 min after administration the antiarrhythmic effect of methacizin did not differ from that of ethacizin alone.

Key Words: *vagus nerve; neurogenic atrial fibrillation; methacizin, ethacizin; ethmozin; neurotropic component of antiarrhythmic effect*

Methacizin is a combined antiarrhythmic preparation containing ethmozin and ethacizin in a 6:1 ratio. This preparation was developed after it had been observed that in patients with monotherapy-insensitive cardiac arrhythmias the antiarrhythmic effect was potentiated by combined treatment with subthreshold doses of ethacizin and ethmozin. In cardiac arrhythmias induced by aconitine, calcium chloride, barium chloride, and coronary occlusion, methacizin by its antiarrhythmic activity was superior to its individual components and the corresponding standard antiarrhythmics.

The present study was aimed at comparison of antiarrhythmic activity of methacizin and its components on modeled neurogenic atrial fibrillations (NAF) [9,10].

MATERIALS AND METHODS

The study was carried out on 22 cats (2.5-4.5 kg) under Chloralose-Nembutal anesthesia (75+15 mg/kg, intraperitoneally). The cats were artificially ventilated and body temperature was maintained at 37°C. NAF were produced and analyzed as described previously [1,4].

Methacizin (n=7), ethacizin (n=7), and ethmozin (n=8) were injected intravenously in doses of 1.4, 0.2, and 1.2 mg/kg, respectively. The data were analyzed statistically with Student's t test.

RESULTS

Despite noticeable individual variability, the experimental groups showed no significant difference in the initial indices of cardiac activity and duration of NAF (Table 1). To compare antiarrhythmic activity of test drugs, their effects were expressed in percent of baseline (Table 2).

Methacizin exerted a negative cardiotropic effect reducing atrial excitability. The prolongation of the effective refractory period and elevation of the atrial excitation threshold lasted for 30 min without affecting myocardial automatism and conductivity. Other preparations exhibited no cardiotropic activity.

All preparations showed a pronounced vagolytic effect and suppressed the chronotropic effect of the vagus nerve (VN). Methacizin, ethacizin, or ethmozin reduced the synchronizing component of the vagal

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chronotropic effect below the control 5, 30, 60, and 120 min postinfusion. The tonic component was affected to a lesser extent, in particular, for ethmozin this reduction was significant only 5 min postinjection.

Similar dynamics was characteristic of antifibrillatory activity of these preparations. Thus, 5 min after methacizin, ethacizin, or ethmozin injection NAF became shorter. The antiarrhythmic effect of methacizin and ethacizin was observed on the following stages of the experiments, while ethmozin exerted only a short-term effect and after 30 min the duration of NAF returned to the baseline values (Table 2).

These data allow us to conclude that the antiarrhythmic effect of methacizin and its components is due to their vagolytic rather than cardiotropic activities. This is in line with our previous findings with

TABLE 1. Initial Cardiac Indices and Duration of NAF during VN Stimulation (*M±m*)

Indices	Initial values
Baseline *RR* intervals, msec	357.7±4.6
Atrial excitation threshold	0.46±0.03
Effective refractory period, msec	137.7±4.1
Sinoatrial conduction, msec	22.9±1.1
PQ interval, msec	73.6±1.5
Vagus nerve excitatiry threshold, V	0.37±0.02
Component of the vagal chronotropic effect, msec synchronizing	264.5±21.0
tonic	85.9±5.5
Duration of atrial fibrillations, sec	203.8±15.9

TABLE 2. Effect of Methacizin and Its Components on Heart Function and Duration of NAF during VN Stimulation (*M±m*)

Indices, %	Preparation	Time after drug administration, min			
		5	30	60	120
Baseline values of *RR* interval	Methacizin	102.8±1.0	101.6±0.3	101.7±1.5	102.1±2.4
	Ethacizin	101.8±1.2	102.7±1.4	100.8±0.6	100.0±1.3
	Ethmozin	100.1±1.3	99.3±0.8	100.4±0.7	100.3±0.3
Atrial excitation threshold	Methacizin	132.4±13.0*	130.0±11.1*	106.1±9.6	113.7±9.4
	Ethacizin	101.6±1.6+	100.7±7.1+	103.6±9.7	103.8±3.3
	Ethmozin	107.2±11.5	99.6±11.5	104.1±7.1	91.6±4.2
Effective refractory period	Methacizin	116.0±3.9*	106.8±2.9*	104.4±4.2	103.1±4.0
	Ethacizin	106.1±2.9	106.4±3.1	103.0±2.0	103.2±2.2
	Ethmozin	101.2±0.9+	100.1±1.2+	100.1±1.2	99.1±1.6
Sinoatrial conduction	Methacizin	100.4±3.2	107.1±6.0	101.0±4.6	95.3±5.6
	Ethacizin	108.4±4.8	102.5±1.7	97.8±3.5	101.7±3.6
	Ethmozin	102.2±2.7	102.5±1.6	101.3±1.3	101.7±1.2
PQ interval	Methacizin	100.5±1.8	102.0±3.9	98.3±2.9	97.6±2.5
	Ethacizin	103.7±3.9	105.8±3.5	101.2±2.5	105.2±3.4
	Ethmozin	103.5±2.3	103.5±2.1	102.8±2.1	102.2±2.4
Vagus nerve excitatory threshold	Methacizin	109.2±4.4	106.5±3.2	101.1±3.5	101.1±3.5
	Ethacizin	104.7±4.7	107.1±7.1	102.3±2.2	102.3±2.2
	Ethmozin	105.0±7.2	109.2±4.8	109.2±4.8	107.3±4.8
Synchronizing component of the vagal chronotropic effect	Methacizin	44.4±8.5*	56.3±8.5*	65.1±9.6*	70.4±11.1*
	Ethacizin	63.1±6.6*	52.4±8.1*	53.0±5.4*	55.8±4.8*
	Ethmozin	60.1±9.5*	60.0±9.5*	59.8±8.8*	57.3±10.1*
Tonic component of the vagal chronotropic effect	Methacizin	51.0±8.7*	69.0±10.5*	73.3±12.3*	76.3±11.6*
	Ethacizin	82.7±5.7*+	82.4±8.1*	82.3±6.8*	80.8±7.8*
	Ethmozin	79.8±8.3*+	80.6±9.6	85.4±9.1	81.6±10.6
Duration of atrial fibrillations	Methacizin	35.8±8.0*	46.1±7.9*	54.0±9.3*	64.4±10.2*
	Ethacizin	57.1±5.3*+	69.9±8.4*	71.6±9.0*	73.0±9.1*
	Ethmozin	74.8±9.9*+	91.1±12.4+	106.1±14.2+	95.8±13.6

Note. $p<0.05$:*in comparison with baseline (100%); +in comparison with methacizin.

respect to novocaine amide, lidocaine, allapinine, cordarone, phencarol and isoptin [1,6-8] and supports the hypothesis on a contribution of negative neurotropic component to antifibrillatory activity of medicinal preparations.

The comparative analysis showed, that under conditions of NAF methacizin is superior by its antiarrhythmic activity to its individual components only during the first 5 min postinjection. At later stages its antifibrillatory activity was primarily determined by ethacizin, while ethmozin exerted only a minor and short-term effect. Similar results were obtained on other models of cardiac arrhythmia [2], where ethacizin was 2- and 5-fold superior to ethmozin by the magnitude and duration of antiarrhythmic activity, respectively. The low antiarrhythmic activity of ethmozin in NAF is due to insufficient and short-term inhibition of vagal tonic influences. In contrast to ethmozin, ethacizin suppressed the tonic component of the vagal effect for a long time and effect did not differ from that of methacizin 30 min postinjection, which agrees with published data [5].

Thus, the inhibitory tonic influence of VN was the key target in the antifibrillatory action of test drugs, while its synchronizing component was equally suppressed by all the drugs throughout the entire observation period. High antiarrhythmic activity of methacizin at the initial stage was due to the additive vagolytic effects of its components rather than their mutual potentiation, at later stages antifibrillatory activity was determined by ethacizin alone.

REFERENCES

1. P. A. Galenko-Yaroshevskii, I. L. Cherednik, V. V. Bartashebich, *et al., Byull. Eksp. Biol. Med.*, **124,** No. 7, 81-85 (1997).
2. N. V. Kaverina, Z. P. Senova, V. V. Lyskovtsev, *et al., Sudden Death* [In Russian], Vil'nyus (1984), pp. 240-249.
3. G. F. Lakin, *Biometry* [in Russian], Moscow (1980).
4. N. B. Leonidov, P. A. Galenko-Yaroshevskii, Yu. R. Sheikh-Zade, *et al., Byull. Eksp. Biol. Med.*, **124,** No. 7, 77-80 (1997).
5. L. V. Rosenshtraukh, F. Urtaler, E. P. Anyukhovskii, *et al., Kardiologiya*, **27,** No. 5, 63-72 (1987).
6. I. L. Cherednik, *Vestn. Aritmol.*, No. 8, 121 (1998).
7. I. L. Cherednik and Yu. R. Sheikh-Zade, *Byull. Eksp. Biol. Med.*, **127,** No. 3, 308-310 (1999).
8. I. L. Cherednik, Yu. R. Sheikh-Zade, and P. A. Galenko-Yaroshevskii, *Ibid.*, No. 2, 174-176.
9. Yu. R. Sheikh-Zade, *Analysis of Cardiac Activity during Vagus Nerve Driving*, Abstract of Doct. Med. Sci. Dissertation, Kiev (1990).
10. Yu. P. Sheikh-Zade and I. L. Cherednik, *Vestn. Aritmol.*, No. 8, 121 (1998).