Antiarrhythmic Effects of KLN-93, Dicaine, and Lidocaine in Neurogenic Atrial Fibrillation

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Antiarrhythmic activities of KLN-93 (crystallographically homogeneous paraaminobenzoic acid ester derivative), dicaine, and lidocaine in cats with neurogenic atrial fibrillation rank in the order in which these agents are named and depend on their vagolytic but not cardiotropic effect whose intensity decreases in the following series: dicaine>lidocaine> KLN-93.

Key Words: *neurogenic atrial fibrillation; local anesthetics; antiarrhythmic effect; vagolytic effect; cardiotropic effect*

Local anesthetics lidocaine, trimecaine, richlocaine, etc., exert antiarrhythmic effect which is determined by molecular structure of these drugs [1,4]. This prompts thorough studies of antiarrhythmic activities of not only known local anesthetics, but also of new compounds with such effects, one of which is crystallographically homogeneous derivative of paraaminobenzoic acid ester (laboratory name KLN-93) prepared at the *Bioeffect* Institute.

An important aspect of the problem is selection of the optimal model of cardiac arrhythmia; we consider neurogenic atrial fibrillation (NAF) easily induced in healthy animals as such a model [5,9,10]. It is maximally similar to natural cardiac rhythm disorders which usually develop in subjects with satisfactory somatic and hemodynamic status. We compared the antiarrhythmic effects of KLN-93, dicaine, and lidocaine in neurogenously induced atrial arrhythmia.

MATERIALS AND METHODS

Experiments were carried out on 36 cats weighing 2.5-4.5 kg narcotized intraperitoneally with Chloralose and Nembutal in doses of 75 and 15 mg/kg, respectively, under conditions of forced ventilation at body temperature 37°C. In all animals the right vagus nerve was cut on the neck; the peripheral end of the nerve was stimulated by an ESU-2 electric stimulator (2 msec, 40 Hz, 6 thresholds) or with a single flash of pulses (2 msec, 40 Hz, 6 thresholds, 3 pulses) synchronously with the *P* wave [5,6]. Bipolar platinum probes were inserted through the right jugular and femoral veins. One probe served as a lead for intra-atrial ECG through cardiosynchronizing block of an original design [8], the other served for stimulation of the atrium (5 msec, 1.5-4.0 threshold) with an ESU-2 stimulator [7]. The ECG was recorded by an N3031-4 automated recorder, the processes were visually assessed using an IM-789 oscillograph.

The duration of the *P-P* (T_o) and *P-Q* intervals, time of sinoatrial conduction of excitation [5,11,12], excitation thresholds for the vagus nerve and atrium, the effective refractory period of the atrium, and synchronizing (within the cycle) and tonic components of the chronotropic effect during stimulation of the vagus nerve with a single flash of pulses were assessed [5,6]. Manifestation of the intracycle component was assessed from the prolongation of the cardiocycle, during which test flash of pulses was delivered, and tonic effect was estimated from the maximum increment of the *P-P* interval during subsequent 2 seconds. For measuring the time of sinoatrial excita-

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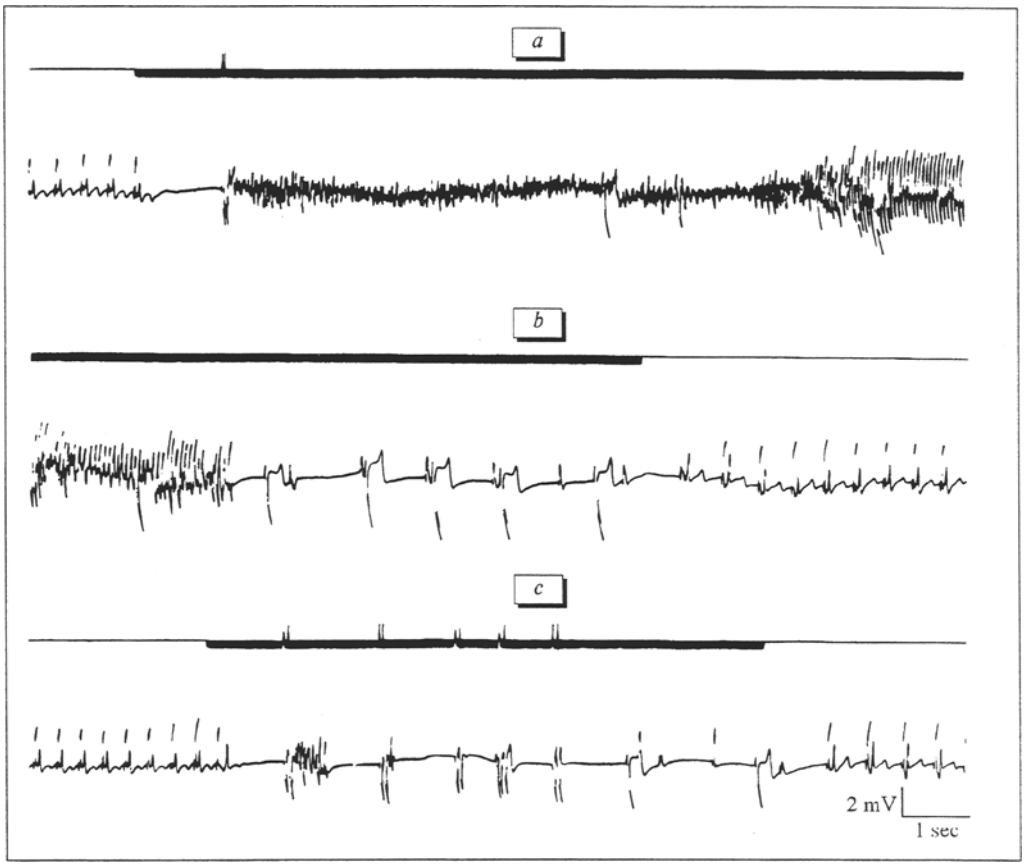

Fig. 1. Antiarrhythmic activity of KLN-93. *a*) induction of neurogenic atrial fibrillation before the drug injection; *b*) spontaneous cessation of paroxysmal arrhythmia 350 sec after its development (see a); *c*) fibrillation cannot be induced 5 min after intravenous injection of the drug. From top to bottom on each fragment: record of atrial stimulation (deviation of the pen upwards) and/or vagus nerve stimulation (deviation of the pen downwards), intra-atrial ECG.

tion conduction, the rhythm of contractions with the T_s interval 5-10% shorter than T_o was imposed on the atrium. After n number of cycles $[n > T_o/(T_o-T_s)]$, atrial stimulation was ceased, and the time of sinoatrial conduction of excitation was measured on the ECG as half of the difference between the (St_n-P_{n+1}) and $(P_{n+2}-P_{n+2})$ intervals, where St_n is the last stimulus.

For inducing NAF, the vagus nerve was continuously stimulated until heart arrest, after which 2 pulses were applied to the atrium (4 thresholds) at 40-msec intervals; as a rule, this induced paroxysmal tachyarrhythmia 30 to 500 sec long (Fig. 1).

The tested agents were injected intravenously in doses of 1 mg/kg (KLN-93, n=16), 1 mg/kg (dicaine, n=10), and 0.35 mg/kg (lidocaine, n=10). The results were statistically processed [3] and the mean arithmetic, mean error, and significance of differences estimated.

RESULTS

The initial values of heart work (the *P-P* and *P-Q* intervals, time of sinoatrial conduction of excitation, effective refractory period, threshold of vagus nerve and atrial excitation) were virtually the same in all series of experiments (p>0.05): 370±10, 72±1, 24±1, 113±3 msec and 0.33±0.01, 0.35±0.03 V (n=36). The expression of the intracycle and tonic components of the vagus nerve chronotropic effect in turn was 187±24 and 62±6 msec, the duration of NAF 112±19 sec.

Five-six minutes after injection of any drug, the duration of NAF dropped (Figs. 1, *c*, 2), reaching the zero level in experiments with KLN-93 and in one experiment with dicaine. After 30 min, NAF failed to develop in 7 cases with KLN-93, in 1 with dicaine, and 1 with lidocaine, after which the antiarrhythmic effect, the longest after KLN-93, declined.

Antifibrillating effects of the studied drugs developed in the presence of a negligible suppression of cardiac activity (Fig. 2): decreased automatism, excitation, and conduction of the myocardium, mainly in cases with dicaine and lidocaine. The suppressive effect of KLN-93 was over as soon as after 30 min, after which heart rate slightly increased.

In addition to cardiotropic effect, all three drugs exerted a potent vagolytic effect, which was the most pronounced in experiments with KLN-93 (Fig. 2).

Comparison of the results of different series of experiments shows that the antifibrillating effect is asso-

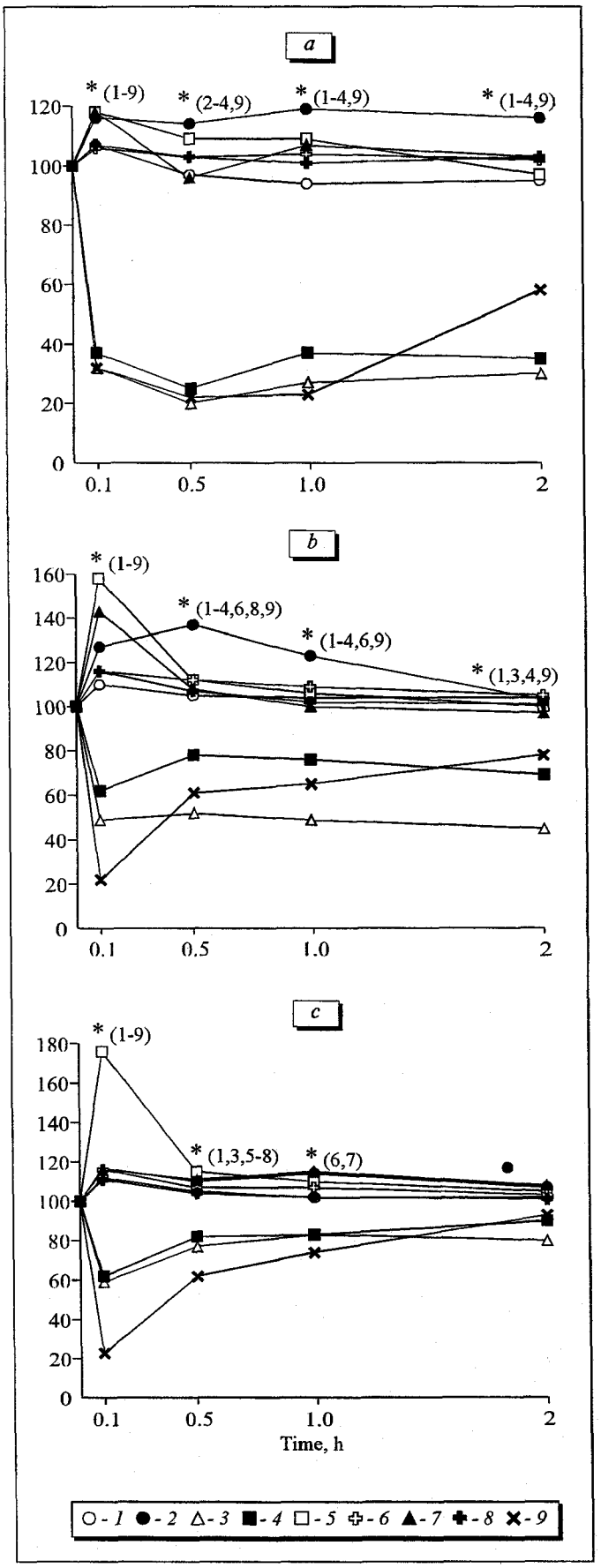

Fig. 2. Time course of antiarrhythmic and cardiotropic effects of KLN-93 (*a*), dicaine (*b*), and lidocaine (*c*). Ordinates: effect, %. *1*) *P-P* interval of the ECG; 2) vagus nerve excitability threshold; synchronizing (*3*) and tonic (*4*) components of the chronotropic effect of the vagus nerve; *5*) atrial excitability threshold; *6*) effective refractory period of the atrium; *7*) time of sinoatrial excitation; *8*) *P-Q* interval; *9*) duration of atrial fibrillation, *$p \leq 0.05$.

ciated with the intensity of cholinolytic but not of cardiotropic effect. This agrees with the hypothesis [5, 9,10] that tachyarrhythmia is caused by critical shortening of the activation-inactivation cycle of the inward potential-dependent ionic currents and of the mechanism of cardiomyocyte membrane repolarization. Such a shortening is possible only during combined exposure to two or more arrhythmogenic factors. During stimulation of vagus nerve the effective refractory period of the atria decreased 4-5 times [7], the decrease being potentiated by extrasystole [5,9,10] caused by the second test pulse 40 msec after stimulation of the stopped heart. As a result, the membrane potential is restored too early, at incomplete inactivation of inward ionic currents, and causes their reactivation and autostimulation of the contractile myocardium. The latter phenomenon can be considered as a regular extrasystole with the characteristic short refractory period [2]. Therefore, if another arrhythmogenic factor is still acting, another autostimulation of the myocardium is possible, and so on, which can be regarded as the trigger or autorhythmic activity.

Thus, autoexcitation of the contractile myocardium ceases if the activation-inactivation cycle of the inward potential-dependent ionic currents (sodium and calcium channel blockers) is decreased or the myocyte (cholinoblockers) repolarization inhibited [5,9,10]

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