Comparative Characteristics of Antiarrhythmic Activity of Phencarol and Dimebone in Neurogenic Ventricular Fibrillation

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The antihistamine drugs (H_1-blockers) dimebone and especially phencarol exhibit antiarrhythmic activity under conditions of neurogenic ventricular fibrillation. The antiarrhythmic activity of phencarol is associated with pronounced vagolytic effect, while that of dimebone is due to both vagolytic and moderate cardiotropic effect.

Key Words: *phencarol; dimebone; neurogenic ventricular fibrillation; vagolytic effect; cardiotropic effect*

The H_1-histamine receptor blockers phencarol (quinuclidyl-3-diphenylcarbinol hydrochloride) and dimebone [3,6-dimethyl-9-(2-methylpyridyl-5)-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride) [2,4] exhibit antiarrhythmic activity in modeled cardiac arrhythmias (CA). For instance, phencarol stops and prevents arrhythmias induced by calcium chloride, adrenalin, and strophanthin without affecting the ECG parameters, heart rate and producing no cardiodepressive effect. The antiarrhythmic activity of phencarol is attributed to its effect not only on H_1-histamine receptors, but also on the cardiomyocyte membrane permeability for calcium ions [9]. Dimebone exerts an antiarrhythmic effect in CA induced not only by chemical agents (adrenalin, strophanthin, calcium and barium chloride), but also by damage to the sinus node (atrial arrhythmia) or by myocardial infarction (ventricular arrhythmias), in some CA being superior or close by its activity and therapeutic range to quinidine, etmozin, bonnecor, and isoptin. The mechanism of this effect includes a primary effect of dimebone on slow calcium channels as well as prolongation of the effective refractory period and inhibition of myocardial conduction [1]. The aim of the present study was to compare antifibrillatory activities of phencarol and dimebon under conditions of neurogenic atrial fibrillation (NAF).

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MATERIALS AND METHODS

The study was performed on 16 cats weighing 2.5-4.5 kg narcotized with Chloralose and Nembutal (75 and 15 mg/kg, respectively) and artificially ventilated; body temperature was controlled automatically (37°C). The right vagus nerve was cut at the level of the thyroid cartilage and its peripheral end was pinned on bipolar needle electrodes (the distance between the poles was 2.5 mm) and embedded into medical wax-vaseline oil mixture. Bipolar platinum probes were inserted into the right ventricle through the right femoral and jugular veins and used for recording the intra-atrial ECG (using an intervalograph assembled in our laboratory [7]) and electrical stimulation. The atrium was stimulated (5 msec, 1.5-4.0 threshold voltage) either in a periodic mode or with singe pulses synchronized with the *P* wave of the ECG using an ESU-2 electrostimulator. The vagus nerve was stimulated in either periodic (2

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TABLE 1. Effect of Phencarol on Heart Function and NAF under Conditions of Vagal Stimulation (VS) in Cats (*M±m*)

Parameter	Initial values	Time postinjection, min				
		5	15	30	60	120
Baseline duration of *P-P* interval, msec	389.0±15.0 (100)	378.0±13.0 (97)	384.0±15.0 (99)	390.0±14.0 (100)	386.0±14.0 (99)	389.0±15.0 (100)
Vagal excitability threshold, V	0.35±0.4 (100)	0.42±0.03* (120)	0.41±0.03 (117)	0.40±0.03 (114)	0.39±0.03 (111)	0.38±0.03 (109)
Synchronizing component of the chronotropic effect of VS, msec	208.0±62.0 (100)	21.0±4.0* (10)	24.0±10.0* (12)	37.0±12.0* (18)	80.0±27.0* (38)	69.0±25.0* (33)
Tonic component of the chronotropic effect of VS, msec	64.0±12.0 (100)	11.0±3.0* (17)	11.0±4.0* (17)	19.0±4.0* (30)	34.0±10.0* (53)	32.0±9.0* (50)
Atrial excitability threshold, V	0.40±0.07 (100)	0.56±0.09* (140)	0.51±0.07* (130)	0.44±0.06 (110)	0.48±0.09 (120)	0.46±0.08 (115)
Effective refractory period of the myocardium, msec	136.0±8.0 (100)	136.0±8.0 (100)	136.0±8.0 (100)	139.0±6.0 (102)	140.0±5.0 (103)	141.0±8.0 (103)
Time of sinoatrial conduction. msec	27.0±2.0 (100)	26.0±2.0 (96)	26.0±2.0 (96)	27.0±3.0 (100)	29.0±2.0 (107)	27.0±2.0 (102)
P-Q interval, msec	73.0±2.0 (100)	75.0±3.0 (102)	75.0±3.0 (102)	74.0±2.0 (101)	76.0±4.0 (103)	74.0±2.0 (101)
Duration of atrial fibrillation, sec	196.0±55.0 (100)	4.0±0.02* (2)	15.0±9.0* (8)	29.0±14.0* (15)	31.0±12.0* (16)	52.0±26.0* (27)

Note. Here and in Table 2: percentage is given in parentheses; *$p \leq 0.05$ compared with the initial values.

TABLE 2. Effect of Dimebon on Heart Function and NAF under Conditions of Vagal Stimulation (VS) in Cats (*M±m*)

Parameter	Initial values	Time postinjection, min				
		5	15	30	60	120
Baseline duration of *P-P* interval, msec	400.0±16.0 (100)	431.0±12.0 (108)	451.0±12.0* (113)	450.0±17.0* (112)	431.0±9.0* (108)	440.0±14.0* (110)
Vagal excitability threshold, V	0.37±0.05 (100)	0.40±0.05 (108)	0.36±0.04 (97)	0.37±0.04 (100)	0.39±0.06 (105)	0.38±0.05 (103)
Synchronizing component of the chronotropic effect of VS, msec	272.0±42.0 (100)	138.0±41.0* (51)	151.0±34.0* (56)	164.0±31.0* (60)	193.0±37.0* (71)	211.0±40.0* (78)
Tonic component of the chronotropic effect of VS, msec	72.0±10.0 (100)	34.0±3.0* (47)	46.0±10.0* (64)	46.0±7.0* (64)	52.0±7.0* (72)	54.0±7.0* (75)
Atrial excitability threshold, V	0.28±0.04 (100)	0.48±0.07* (171)	0.32±0.02 (114)	0.30±0.05 (107)	0.31±0.04 (111)	0.29±0.04 (104)
Effective refractory period of the myocardium, msec	129.0±5.0 (100)	153.0±6.0* (119)	148.0±8.0* (115)	148.0±6.0* (115)	154.0±6.0* (119)	147.0±6.0* (114)
Time of sinoatrial conduction, msec	23.0±2.0 (100)	31.0±2.0* (135)	27.0±3.0 (117)	24.0±2.0 (104)	23.0±2.0 (100)	23.0±2.0 (100)
P-Q interval, msec	74.0±3.0 (100)	86.0±5.0* (116)	78.0±4.0* (105)	76.0±3.0 (103)	74.0±3.0 (100)	74.0±3.0 (100)
Duration of atrial fibrillation, sec	122.0±32.0 (100)	20.0±6.0* (16)	36.0±10.0* (30)	66.0±18.0* (54)	69.0±16.0* (57)	95.0±24.0* (78)

msec, 40 Hz, 6 threshold voltage) or single mode Visual control was carried out using an 8-channel IM-789 oscillograph.

The following parameters were assessed: the *P-P* (T_0) and *P-Q* intervals of the ECG, time of sinoatrial conduction [10,11], atrial and vagal excitation thresholds, effective refractory period of the atrium, synchronizing and tonic components of the vagal chronotropic effect under conditions of single-burst stimulation of *n. vagus*. The synchronizing (inter-

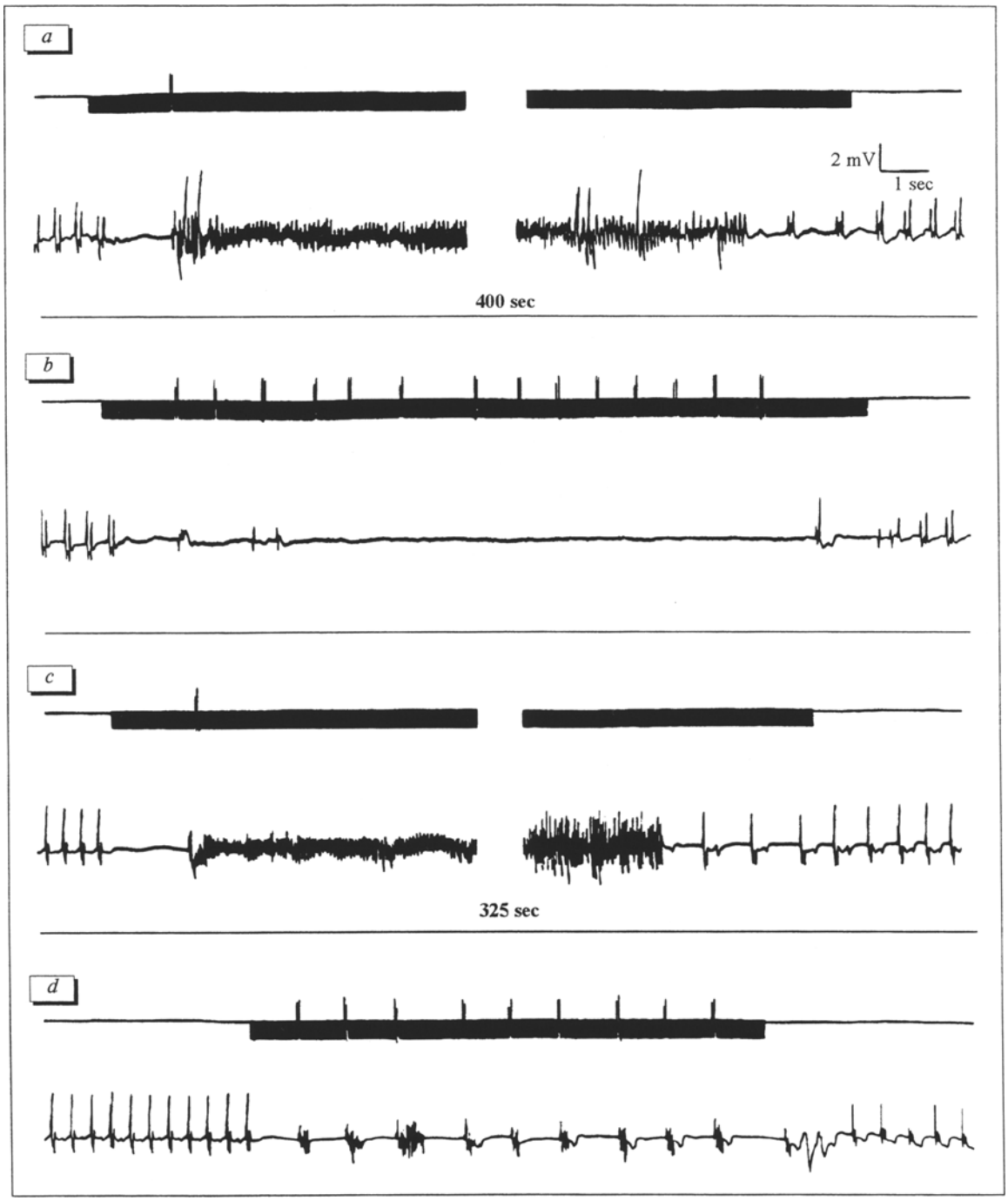

Fig. 1. Antiarrhythmic effect of phencarol and dimebon on cat heart. On each fragment from top to bottom: stimulation of the right atrium and/or vagus nerve (channel 1), intra-atrial ECG (channel 2). Onset and termination (after *a*: 400 sec and *c*: 325 sec) of atrial fibrillation before injection of phencarol (*a*) and dimebon (*c*); the absence of atrial fibrillation 5 min after injection of phencarol (*b*) and dimebon (*d*).

cycle) component was assessed by the lengthening of the atrial cycle coinciding with stimulus delivery, while the tonic component was evaluated by the maximum lengthening of the next atrial cycle.

For evaluation of the time of sinoatrial conduction, the atrium was paced at a rate 5-10% surpassing the baseline heart rate. The stimulation was stopped after n heartbeats ($n > T_o/(T_o - T_{st})$, where T_{st} is the stimulation period, and sinoatrial conduction was determined as the half-difference between intervals ($St_n - P_{n+1}$) and ($P_{n+1} - P_{n+2}$), where St_n is the last stimulating pulse.

For modeling atrial fibrillation, continuous stimulation of the vagus nerve (2 msec, 40 Hz, 6 thresholds) was used, and against the background of cardiac arrest 2 pulses (5 msec, 4 thresholds) were delivered

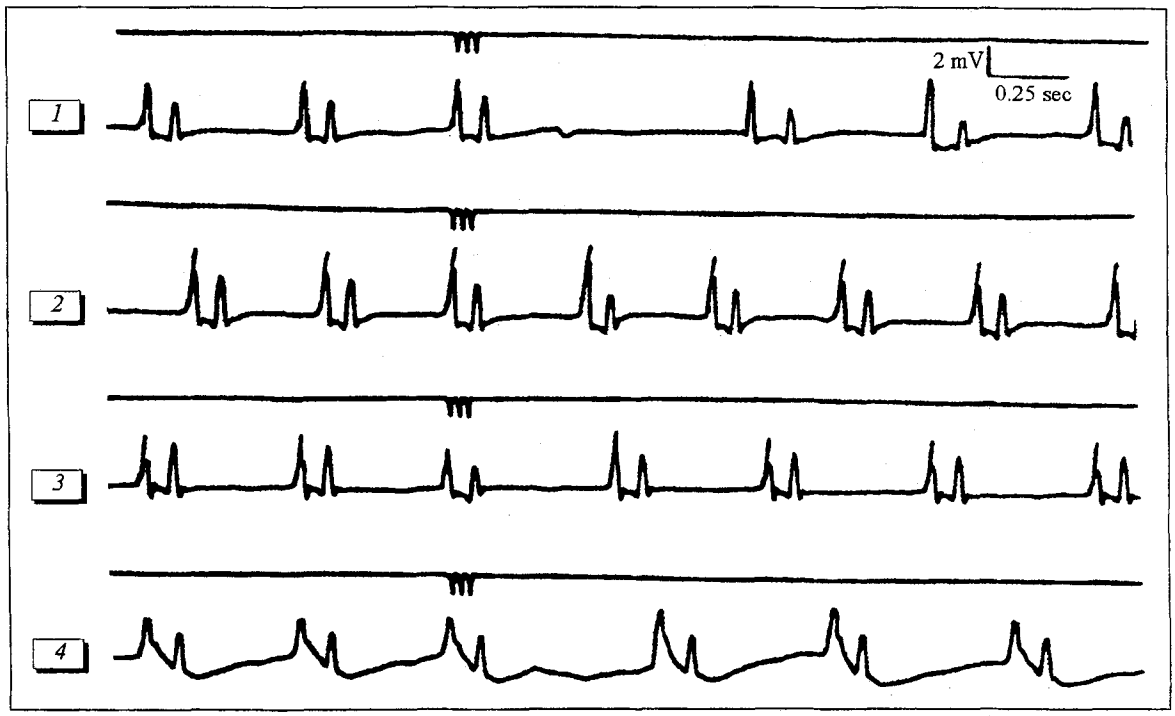

Fig. 2. Dynamics of vagolytic effect of phencarol. On each fragment from top to bottom: vagal stimulation mark (2 msec, 40 Hz, 6 thresholds, bursts of 3 pulses) and intra-atrial ECG. Chronotropic effect of the vagus nerve stimulated with single bursts of pulses before (*1*) and 5 (*2*), 15 (*3*), and 120 (*4*) min after injection of phencarol.

to the right atrium at an interval of 40 msec [5]. The duration of fibrillation paroxysm was measured, and the nerve stimulation was terminated.

Phencarol (n=7) and dimebon (n=9) were injected intravenously in a dose of 5 mg/kg.

The data were processed using routine statistical methods.

RESULTS

Five min after phencarol and dimebon infusion a shortening of NAF was noted (Tables 1 and 2). At this stage of the experiment, only in 2 cases with phencarol a short-term fibrillation paroxysm was induced, while in other cases NAF was absent (Fig. 1). Dimebon also sharply reduced the duration of NAF and even prevented it in experiment 1 (Fig. 1). Fifteen minutes postinjection NAF was absent in 3 experiments with phencarol and in 1 experiment with dimebon. At the subsequent stages the antifibrillatory effect of phencarol and especially dimebon gradually decreased.

The antiarrhythmic effect of phencarol was associated with pronounced vagolytic effect which manifested itself as a marked decrease of the synchronizing and tonic components of the vagal chronotropic effect (Fig. 2). A direct dependence was noted between the vagolytic effect of phencarol and the duration of fibrillation. For instance, the decreased synchronized and tonic vagal influences were somewhat restored as soon as 15 min postinjection, which led to a decrease in its antifibrillatory effect. This correlation was also observed during subsequent stages of the experiment. On the other hand, phencarol exerted no distinct cardiotropic effect and had no effect on effective refractory period, cardiac conduction, and automaticity. Hence, the major antiarrhythmic effect of phencarol can be attributed to its vagolytic effect, which prevents neurogenic activation of outward ionic currents and, therefore, accelerates repolarization of the contractile myocardium [3,8]. This phenomenon is of particular interest, since phencarol is considered to possess no cholinolytic effect [2].

The antiarrhythmic activity of dimebon is due to a combination of its cholinolytic and moderate cardiotropic effects. The latter manifests itself in a considerable inhibition of cardiac automaticity and negative dromo- and batmotropic effects (Table 2). For instance, dimebon prolongs the effective refractory period of the atria, which is indicative of inhibition of repolarization of the myocardium. On the basis of our previous hypothesis [3,8] the antiarrhythmic effect of dimebon can be attributed to the shortening of the activation-inactivation cycle of voltage-dependent inward ionic currents, direct prolongation of the effective refractory period, and blockage of arrhythmogenic influence of the vagus nerve [3].

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