PHARMACOLOGY AND TOXICOLOGY

Antiarrhythmic Effect of GABA Derivative TZ-50-2 in Neurogenic Atrial Fibrillation

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In experiments on anesthetized cats, GABA derivative TZ-50-2 (4-oxy-3-benzylamino-N-benzylbutanamide hemisuccinate) produced a pronounced antiarrhythmic effect during neurogenic atrial fibrillation, in which the key role was played by a depriming action on vagal innervation of the heart.

Key Words: *vagus; neurogenic atrial fibrillation; GABA; antiarrhythmic effect; neurotropic influence*

A pronounced antiarrhythmic effect of TZ-50-2 (4-oxy-3-benzylamino-N-benzylbutanamide hemisuccinate) was demonstrated on various models of atrial, ventricular, and atrioventricular cardiac rhythm disturbances [1]. The objective of the present study was to evaluate antiarrhythmic activity of TZ-50-2 in neurogenic atrial fibrillation (NAF) [5,6], recommended by Pharmacological Committee of Ministry of Health as the standard test for potential antiarrhythmic drugs [3].

MATERIALS AND METHODS

The antiarrhythmic effect of TZ-50-2 (5 mg/kg intravenously) was studied on 8 cats narcotized intraperitoneally with Chloralose-Nembutal mixture (75 and 18 mg/kg, respectively) and artificially ventilated. Bipolar platinum probes were introduced transvenously into the right atrium to stimulate myocardium with an ESU-2 stimulator (Kursk) and to record intracardial ECG [4] by an N-338 recorder (Krasnodar). NAF was provoked by paired atrial stimulation (5 msec, 4-fold threshold value, 25 Hz) applied against the background of supramaximal stimulation of the right vagus nerve on the neck (2 msec, 6-fold threshold value, 40 Hz) performed with another ESU-2 stimulator via bipolar platinum electrodes (2 mm between tips). The vagal chronotropic effect was assessed by elongation of *PP* interval on ECG induced by a single train of 3 pulses (2 msec, 6-fold threshold value, 40 Hz) presented synchronously with the *P* peak. Visual control of the signals was performed with an IM-789 Oscilloscope (Lithuania).

RESULTS

Injection of TZ-50-2 immediately and strongly suppressed NAF, enhanced the atrial excitation threshold, and prolonged *PP* and *PQ* intervals on ECG and the effective refractory period of the myocardium (Table 1). Two hours postinjection the automaticity, excitability, and conduction parameters of the myocardium returned to normal, while NAF was suppressed in comparison with the initial value (Table 1). These data and drastic decrease in the chronotropic effect of the vagus nerve throughout the experimental period show that the key role in the antiarrhythmic effect of TZ-50-2 is played by its neurotropic (cholinoblocking),

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TABLE 1. Effect of TZ-50-2 on Vagal and Cardiac Activity ($M \pm m$, n=8)

Indices	Initial values	Time postinjection, min			
		5	30	60	120
Background *PP* interval of ECG, msec	348±8 (100)	394±9* (113)	370±8* (106)	368±15 (106)	362±13 (104)
Atrial excitability threshold, mV	550±60 (100)	640±80* (116)	390±50* (71)	450±50 (82)	500±50 (91)
Atrial effective refractory period, msec	138±4 (100)	164±5* (119)	154±6* (112)	155±7* (112)	146±8 (106)
Sinoatrial conduction time, msec	18±1 (100)	20±2 (111)	18±2 (100)	18±1 (100)	18±1 (100)
PQ interval, msec	73±2 (100)	78±2* (107)	74±2 (101)	74±2 (101)	73±2 (100)
Vagal excitability threshold, mV	380±40 (100)	460±20* (121)	420±40* (110)	430±50 (113)	410±50 (108)
Vagal chronotropic effect, msec	258±27 (100)	129±11* (50)	152±23* (59)	151±22* (59)	181±28* (70)
Duration of neurogenic atrial fibrillation, sec	139±8 (100)	3±2* (2)	54±8* (39)	102±15* (73)	114±13* (82)

Note. *$p<0.05$ compared to the initial values. Percent of changes is given in parentheses.

rather than cardiotropic effect on the neural cardiac apparatus. It cannot be excluded that the conduction disturbances in sympathetic ganglia play a role in the antiarrhythmic effect of TZ-50-2 [2]. In this case, the TZ-50-2-induced decrease in excitability and conduction of the myocardium can be explained not only by direct, but also indirect effect on the heart rate and trophic action of the nervous system.

These data agree with our hypothesis [7], that antiarrhythmic drugs produce their effect primarily via blockage of the neural cardiac apparatus, whose dysfunction is first and foremost reason of natural (not experimental) disturbances in the cardiac rhythm.

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