Antiarrhythmic Activity of Amiodarone in Neurogenic Atrial Fibrillations

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 127, No. 3, pp. 308-310, March, 1999
Original article submitted May 14, 1998

Acute experiments on cats showed that dynamics of amiodarone antiarrhythmic activity with respect to neurogenic atrial fibrillations correlates with its neurotropic effects rather than its cardiotropic activity.

Key Words: *vagus nerve; neurogenic atrial fibrillation; amiodarone; neurotropic component of antiarrhythmic activity; cardiotropic effect*

Amiodarone is a potent antiarrhythmic drug with unique pharmacokinetic characteristics [10]. It exerts pronounced effects on cardiac arrhythmias caused by aconitine, glycoside, barium chloride, acetylcholine [8,9], and by occlusion and reperfusion of the coronary artery [5,6,13]. Amiodarone is assigned to the class III antiarrhythmics [14] that prolong the action potential and the effective refractory period (ERP) of cardiomyocytes. However, the antiarrhythmic effect of amiodarone includes also electrophysiological effects, typical of other antiarrhythmics, such as suppression of fast sodium current, blockade of membrane calcium channels, and adrenolytic effects [2,4,11,12]. The pharmacological profile of amiodarone antiarrhythmic activity has not been sufficiently studied, and experimental data are controversal and difficult to interprete because of artificial cardiac arrhythmia models used in the majority of studies.

Our aim was to study the antiarrhythmic effects of amiodarone on neurogenic atrial fibrillation (NAF) [7] in healthy animals. The controllable nature of NAF makes it an appropriate model for studying the mechanisms of endogenous cardiac arrhythmias.

MATERIALS AND METHODS

The study was carried out on 9 artificially ventilated cats (2.5-4.5 kg body weight) under Chloralose-Nembutal anesthesia (75+15 mg/kg intraperitoneally). Body temperature was maintained at 37°C. Neurogenic atrial fibrillation was induced and analyzed as described elsewhere [3]. Amiodarone was injected intravenously in a dose of 5 mg/kg. The data were analyzed statistically using Student's t test.

RESULTS

Five minutes after amiodarone injection, the cardiac cycles became longer with simultaneous prolongation of atrial ERP and PQ intervals of the ECG (Table 1). This negative cardiotropic effect of the drug on atrial automatism and excitability as well as on atrioventricular conduction lasted for 1 h.

Amiodarone showed pronounced vagolytic activity increasing the vagus nerve excitatory threshold (30 min) and suppressing the vagal chronotropic effect. Five minutes after the drug infusion, both the synchronizing and tonic components of the chronotropic effect decreased considerably. Although weakened later, these manifestations of vagolytic activity persisted throughout the observation period (Table 1).

As expected, amiodarone exhibited high antifibrillatory activity under conditions of NAF: the duration of fibrillation considerably decreased 5 min postinjection and was completely absent in 3 experiments.

It can be concluded that the antifibrillatory effect of amiodarone results from its pronounced neurotropic activity rather than from negative cardiotropic activity.

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0007-4888/99/0003-0278$22.00

TABLE 1. Effects of Amiodarone on Cardiac Function and Atrial Fibrillations Caused by Vagus Nerve Stimulation in Cats (*M±m*, *n*=9)

Parameters	Initial values	Changes in the indices during the experiment, min			
		5	30	60	120
Baseline duration of *R-R* interval, msec	370.0±6.8	464.4±20.8 (125.5)*	442.2±19.6 (119.5)*	425.5±20.2 (115)*	393.3±18.7 (106.2)
Vagus nerve excitatory threshold, V	0.40±0.03	0.46±0.04 (115)*	0.45±0.04 (112.5)*	0.41±0.03 (102.5)	0.42±0.02 (105)
Components of the vagal chronotropic effect, msec					
synchronizing	244.4±28.1	117.7±22.3 (48.2)*	151.1±33.6 (61.8)*	166.6±31.9 (68.1)*	155.5±32.4 (63.6)*
tonic	84.4±14.7	28.8±3.5 (34.1)*	38.8±5.1 (45.9)*	47.2±8.5 (55.9)*	42.2±4.0 (50)*
Atrial excitation threshold	0.35±0.02	0.45±0.06 (128.6)	0.40±0.04 (114.2)	0.35±0.03 (100)	0.33±0.03 (94.3)
ERP of myocardium, msec	138.8±7.9	172.2±9.9 (124)*	165.0±8.7 (118.8)*	157.7±7.9 (113.6)*	147.7±7.7 (106.4)
Sinoatrial conduction, msec	19.5±2.1	20.2±2.0 (103.5)	19.5±1.8 (100)	18.2±1.7 (93.3)	18.0±1.4 (92.3)
PQ interval, msec	72.0±2.7	82.6±4.4 (114.7)*	80.4±4.6 (111.6)*	75.1±3.6 (104.3)*	72.4±2.9 (100.5)
Duration of atrial fibrillation, sec	261.7±58.9	32.2±11.3 (12.3)*	72.2±21.9 (27.5)*	110.5±32.8 (42.2)*	111.1±32.1 (42.5)*

Note. Figures in parentheses represent the percentage of the initial values (100%), * $p \leq 0.05$ in comparison with the initial values.

This fact is of special interest, since previous studies did not concentrate on amiodarone anticholinergic activity and attributed its antiarrhythmic activity to an increase in ERP. Another explanation was based on the correlation between the antiarrhythmic potency of amiodarone and prolongation of the cardiomyocyte action potentials [2]. At the same time, the increase in atrial and ventricular ERP was reported only after peroral, but not intravenous administration of amiodarone [15]. It has been suggested, therefore, that some other mechanisms, different from ERP prolongation, are implicated in the antiarrhythmic activity of amiodarone [1]. It can be assumed that the neurotropic component plays a key role in the antifibrillatory effect of amiodarone *in situ*, since the suppression of NAF coincides with anticholinergic manifestations and lasts over 2 h, when all cardiotropic effects become insignificant.

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