The Role of Neurotropic Component in Therapeutic Effect of Antiarrhythmic Drugs

Yu. R. Sheikh-Zade, I. L. Cherednik, and P. A. Galenko-Yaroshevskii

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 127, No. 3, pp. 353-356, March, 1999
Original article submitted May 14, 1998

Acute experiments on anesthetized cats with neurogenic atrial fibrillation showed that the antifibrillatory effect of procainamide, lidocaine, and ethacizin correlated with their vagolytic rather than with cardiotropic activity.

Key Words: *vagus nerve; neurogenic atrial fibrillation; lidocaine; procainamide; ethacizin; neurotropic component of antiarrhythmic effect*

Although the nature of cardiac tachyarrhythmia and the ways to treat it were discussed for many years, these problems are far from being completely understood. One of the reasons of this impasse may be an artificial character of most experimental arrhythmia models, which are only a rough approximation of natural conditions. Another shortage of such models is their uncontrollable character that excludes the possibility to observe the dynamics of antiarrhythmic effects. In light of this, the neurogenic atrial fibrillation (NAF) induced in healthy animals without pharmacological intervention [12,13] is of great interest. In addition, NAF is controllable and therefore provides better approximation to the natural mechanisms of atrial tachyarrhythmias.

Our aim was to compare the pharmacological activity of three representative class I antiarrhythmic drugs [14]: procainamide (subclass IA), lidocaine (subclass IB), and ethacizin (subclass IC) under conditions of NAF.

MATERIALS AND METHODS

Experiments were carried out on 28 cats (body weight 2.5-4.5 kg) narcotized intraperitoneally with Chloralose-Nembutal mixture (75 and 15 mg/kg, respectively) and artificially ventilated; body temperature was 37°C. The methods of inducing and analyzing NAF are described in details elsewhere [2,6,12,13].

Procainamide (n=8), lidocaine (n=10) and ethacizin (n=10) were injected intravenously in doses of 15, 3.5, and 1 mg/kg, respectively. The results were statistically analyzed using Student's t test [5].

RESULTS

The cardiotropic effects of the studied drugs differed considerably at different stages of the experiment. Lidocaine decreased automatism and atrial excitability and impaired atrioventricular and sinoatrial conduction. The effective refractory period of the atria and the time of sinoatrial conduction were prolonged as long as 1 h postinjection, while other parameters (*P-P* and *P-Q* intervals and atrial thresholds) returned to their initial values. Procainamide also prolonged PP and PQ intervals to 60 and 30 min, respectively, elevated the atrial excitation threshold (for up to 30 min) and prolonged the effective refractory period (for less than 30 min). Ethacizin had practically no effect on automatism, excitability and conduction in the myocardium, but slightly inhibited sinoatrial conduction (<30 min).

In addition to the described effects, all test drugs had pronounced vagolytic activity: they elevated the excitability threshold of the vagus nerve (VN) and moderated its synchronizing and tonic effects [10]. The inhibition of chronotropic effects with procain-

Department of Normal Physiology, Kuban Medical Academy, Krasnodar

0007-4888/99/0003-0320$22.00

amide and ethacizin was observed at all stages of the experiment, while lidocaine inhibited the tonic and synchronizing effects of VN during 5 and 30 min, respectively.

The duration of NAF decreased by 88.3, 76.6, and 64.8% 5 min after injection of procainamide, lidocaine, and ethacizin, respectively. Two hours later the effects of procainamide and ethacizin were maintained, although in a lesser degree (Tables 1 and 3). The antiarrhythmic effect of lidocaine was shorter, so the duration of NAF did not differ from the baseline value to the end of the 1st hour postinjection (Table 2).

The antiarrhythmic effects of the test drugs correlate with their vagolytic, rather than cardiotropic activity. This is an unexpected conclusion, because most papers stress that the main effect of class I antiarrhythmic drugs is inhibition of fast Na^+ current in cardiomyocytes [7,8,14]. However, our experiments showed that the therapeutic effect of these agents is more complex and versatile. Presumably, the inhibition of fast Na^+ current occurs not in myocytes, but predominantly in neurons of the autonomic nervous system that mediate arrhythmogenic influences to myocardium. For example, pronounced vagal activity provokes premature atrial repolarization [1,3,12,13], while the effect of catecholamines or sympathetic nerves results in activation of inward ionic currents leading to early or delayed myocardial postdepolarization [1,15]. In both cases progressive decrease of myocardial excitation threshold occurs [1,11]. Therefore, the critical convergence of inward and outward ionic currents may decrease the depolarization threshold to zero and induce trigger-like self-excitation of the myocardium. Since parasympathetic ventricular innervation is limited, this type of arrhythmia takes place primarily in the atria, which agrees with published data [4].

This approach clarifies the correlation between the antiarrhythmic and local anesthetic properties of many antiarrhythmic drugs [1,7,8], because inhibition of the afferent link contributes into the therapeutic effect of these agents by suppressing the reflector mechanisms of the arrhythmogenic effects of the autonomic nervous system.

Our data indicate that the effect of other class I antiarrhythmic drugs [6], as well as propranolol, amiodarone, and verapamil [9] (belonging to classes II-IV according to classification [14]) is also mediated via negative neurotropic action on sympathetic and/or parasympathetic structures in the heart. A similar effect was found for antihistamine drugs phencarol and dimebon that have pronounced antiarrhythmic potency [2].

Therefore, the antiarrhythmic effect of many (if not all) medical preparations includes pronounced negative neurotropic component, and the correct theory of

TABLE 1. Effect of Procainamide on Heart Function and Duration of Atrial Fibrillation under Conditions of Vagal Stimulation (VS) in Cats ($M \pm m$, $n=8$)

Parameter	Initial values	Time postinjection, min			
		5	30	60	120
Baseline duration of *P-P* interval, msec	358.8±6.9	387.5±7.7* (107.9)	388.7±5.5* (108.3)	373.7±6.8* (104.1)	352.2±7.0 (98.2)
Vagal excitability threshold, V	0.51±0.03	0.61±0.04* (119.4)	0.60±0.04* (117.6)	0.57±0.04 (111.7)	0.53±0.03 (103.9)
Components of the chronotropic effect of VS, msec					
synchronizing	218.8±33.7	75.0±20.1* (34.2)	95.0±28.4* (43.4)	116.2±35.5* (53.1)	123.1±32.7* (56.2)
tonic	71.3±9.2	26.2±7.0* (36.7)	36.2±8.8* (50.7)	41.2±10.6* (57.7)	46.2±9.0* (64.7)
Atrial excitability threshold, V	0.39±0.03	0.63±0.05* (161.5)	0.57±0.05* (146.1)	0.45±0.02 (115.3)	0.40±0.03 (102.5)
Effective refractory period of the myocardium, msec	138.1±6.9	150.0±7.0* (108.6)	146.3±6.6 (105.9)	146.8±6.4 (105.8)	140.6±5.8 (101.3)
Duration of sinoatrial conduction, msec	19.5±0.3	20.2±0.6 (103.5)	20.5±0.7 (105.1)	20.2±0.8 (103.5)	20.5±0.9 (105.1)
P-Q interval, msec	68.5±2.4	72.0±3.6* (105.1)	72.5±3.3* (105.8)	70.5±2.6 (102.9)	67.4±1.6 (98.4)
Duration of atrial fibrillation, msec	120.6±40.8	14.2±7.2* (11.7)	41.0±14* (33.9)	42.5±12.7* (35.2)	50.3±14.8* (41.7)

Note. Here and in Table 2: percentage of initial value is given in parenthesis; * $p<0.05$ compared with the initial values.

TABLE 2. Effect of Lidocaine on Heart Function and Duration of Atrial Fibrillation under Vagal Stimulation (VS) in Cats (*M±m*, *n*=10)

Parameter	Initial values	Time postinjection, min			
		5	30	60	120
Baseline duration of *P-P* interval, msec	383.0±11.9	429.0±18.3* (112)	401.0±18.3* (104.6)	391.0±14.0 (102)	390.0±26.2 (101.8)
Vagal excitability threshold, V	0.29±0.02	0.34±0.01* (117.2)	0.32±0.01 (110.3)	0.33±0.01 (113.7)	0.31±0.02 (106.8)
Components of the chronotropic effect of VS, msec					
synchronizing	209.0±37.8	123.0±23.8* (58.8)	160.0±30.3* (76.5)	173.0±34.6 (82.7)	166.6±38.2 (79.7)
tonic	65.0±15.4	40.0±6.4* (61.5)	53.0±9.7 (81.5)	54.0±10.8 (83)	58.3±14.3 (89.6)
Atrial excitability threshold, V	0.41±0.06	0.72±0.19* (175.6)	0.47±0.06* (114.6)	0.45±0.04 (109.7)	0.43±0.04 (104.8)
Effective refractory period of the myocardium, msec	115.5±8.1	134.0±8.1* (116)	124.0±6.4* (107.3)	123.5±7.5* (106.9)	118.8±7.7 (102.8)
Duration of sinoatrial conduction, msec	22.8±1.7	26.4±1.2* (115.7)	25.4±1.7* (111.4)	26.2±2.1* (114.9)	24.7±2.2 (108.3)
P-Q interval, msec	70.4±2.1	78.4±3.0* (111.3)	73.2±3.0* (103.9)	72.0±2.1 (102.2)	71.1±2.3 (100.9)
Duration of atrial fibrillation, msec	127.0±31.9	29.8±5.3* (23.4)	78.7±19.4 (61.9)	94.3±17.3 (74.2)	118.0±40.5 (92.9)

TABLE 3. Effect of Ethacizin on Heart Function and Duration of Atrial Fibrillation under Vagal Stimulation (VS) in Cats (*M±m*, *n*=10)

Parameter	Initial values	Time postinjection, min			
		5	30	60	120
Baseline duration of *P-P* interval, msec	371.0±5.4	369.0±5.0 (99.5)	375.0±6.7 (101)	370.0±5.9 (99.7)	370.0±5.1 (99.7)
Vagal excitability threshold, V	0.36±0.02	0.42±0.03* (116.6)	0.42±0.02* (116.6)	0.40±0.02* (111.1)	0.38±0.02 (105.5)
Components of the chronotropic effect of VS, msec					
synchronizing	260.0±26.4	131.0±17.6* (50.3)	127.0±17.9* (48.8)	143.0±21.9* (55)	159.0±25.5* (61.1)
tonic	84.0±6.0	52.0±5.3* (61.9)	56.0±4.2* (66.6)	54.0±4.0* (64.2)	63.0±8.3* (75)
Atrial excitability threshold, V	0.42±0.04	0.44±0.04 (104.7)	0.45±0.05 (107.1)	0.36±0.03 (85.7)	0.35±0.03* (83.3)
Effective refractory period of the myocardium, msec	135.5±3.2	136.0±3.6 (100.3)	138.8±3.0 (102.4)	137.5±3.8 (101.4)	134.5±3.8 (99.2)
Duration of sinoatrial conduction, msec	19.0±1.3	20.4±1.6* (107.3)	19.2±1.0 (101)	17.8±0.5 (93.6)	17.6±0.6 (92.6)
P-Q interval, msec	71.2±1.7	72.0±2.1 (101.1)	70.0±1.9 (98.3)	70.4±2.0 (98.8)	69.6±2.1 (97.7)
Duration of atrial fibrillation, msec	178.5±20.8	63.0±2.0* (35.2)	101.5±25.3* (56.8)	125.0±24.6* (70)	137.5±22.8* (77)

therapeutic efficiency of antiarrhythmic drugs cannot be constructed without this component. Logically, there is a good reason to perform screening for new antiarrhythmic agents under conditions of NAF and to refine the machanism of their pharmacological action.

REFERENCES

1. W. J. Mandel (Ed.), *Cardiac Arrhythmias: Their mechanisms, Diagnosis and Management*, London (1987).
2. P. A. Galenko-Yaroshevskii, I. L. Cherednik, V. V. Bartashevich, *et al.*, *Byull. Eksp. Biol. Med.*, **124**, No. 7, 81-85 (1997).
3. B. F. Hoffman and P. F. Cranefield, *Electrophysiology of the Heart*, New York (1960).
4. M. S. Kushakovskii, *Kardiologiya*, **24**, No. 5, 5-10 (1984).
5. G. F. Lakin, *Biometry* [in Russian], Moscow (1980).
6. N. B. Leonidov, P. A. Galenko-Yaroshevskii, Yu. R. Sheikh-Zade, *et al.*, *Byull. Eksp. Biol. Med.*, **124**, No. 7, 77-80 (1997).
7. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 1, Moscow (1997), p. 370.
8. V. I. Metelitsa, *Reference Book on Clinical Pharmacology of Cardiovascular Drugs* [in Russian], Moscow (1996).
9. I. L. Cherednik, *Vestn. Aritmol.*, No. 8, 121 (1998).
10. Yu. R. Sheikh-Zade, *Fiziol. Zh. SSSR.*, **67**, No. 7, 1027-1034 (1981).
11. Yu. R. Sheikh-Zade, *Ibid.*, **73**, No. 5, 672-674 (1987).
12. Yu. R. Sheikh-Zade, *Analysis of Heart Function Paced with Vagal Stimulation Rhythm*, Abstract of Doct. Med. Sci. Dissertation, Kiev (1990).
13. Yu. R. Sheikh-Zade and P. A. Galenko-Yaroshevskii, *Byull. Eksp. Biol. Med.*, **104**, No. 9, 261-263 (1987).
14. E. M. Vaughan-Williams, *Pharmacol. Ther.*, **1**, 115-138 (1975).
15. D. P. Zipes, *Prog. Cardiovasc. Dis.*, **3**, No. 6, 385-396 (1991).