A New Method for Evaluation of Safety of Antiarrhythmic Drugs

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A new method for preclinical evaluation of safety of antiarrhythmic drugs is proposed. During chronic stress, class I antiarrhythmic preparations increased mortality of test animals. By contrast, class II-IV antiarrhythmic agents and antioxidants produced no significant effect on mortality of experimental mice. These data agree with published results of multicenter studies.

Key Words: *antiarrhythmic drugs; toxicity*

Some studies showed that some antiarrhythmic drugs increase mortality of patients with cardiovascular pathology [8,9,15]. This fact indicates that modern methods of preclinical testing of potential antiarrhythmic drugs do not prognosticate reliably the safety of these preparations. This can be explained by the fact that according to modern standards, toxicological tests are conducted on healthy animals.

In light of this, the aim of the present study was to develop a simple and inexpensive model for testing safety of long-term antiarrhythmic therapy.

MATERIALS AND METHODS

Experiments were carried out on outbred mice (n= 656) weighing 18-22 g. Group 1 mice were kept in standard cages for 1.5 months. Group 2 animals were subjected to immobilization stress: the mice were placed in narrow (40 cm^3) plastic cylinders for 6 hours 6 times per week.

Antiarrhythmic drugs ethmozine (2 mg/kg), ethacizin (0.5 mg/kg), lidocaine (10 mg/kg), propranolol (0.5 mg/kg), amiodarone (the first injection 7.5 mg/kg, the following daily injections of 5.0 mg/kg), quaternidine (2 mg/kg), and verapamil (0.5 mg/kg), and antioxidants mexidol (20 mg/kg), cytochrome-c (20 mg/kg), and dimephosphon (100 mg/kg) were injected intraperitoneally in 0.2 ml NaCl saline (0.9%). The control mice received placebo (0.9% NaCl).

In the first series, the test antiarrhythmic agents and antioxidants were administered to healthy animals (20 mice per series) not subjected to chronic stress.

In the second series, the preparations were injected in the same doses to mice subjected to chronic stress.

The results were analyzed statistically using χ^2 test.

RESULTS

In the first series 2 mice died in the ethmozine and 2 in the dimephosphon groups (p>0.05), no mortality was observed in the placebo and other treatment groups. These results agree with the data on chronic toxicity submitted by the drug-makers to Russian Drug Administration.

During chronic stress, the toxic properties of some drugs changed significantly.

Chronic stress significantly increased mortality in mice treated with lidocaine, ethmozine, and ethacizin (p<0.05, Table 1). Mortality in the group receiving propranolol increased insignificantly. Similar results were obtained with long-term administration of amiodarone, quaternidine, and verapamil (Table 1).

The test antioxidants were safe; cytochrome-c even decreased animal mortality (Table 1).

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Our data agree with the results of clinical observations (Table 2). Surprisingly, repeated injection of lidocaine during chronic stress increased animal mortality. This effect was not observed in clinical studies, probably because this drug is never applied to prevent arrhythmia at the postclinical stage due to its specific pharmacokinetics [3]. However, published data suggest that long-term administration of lidocaine to patients with myocardial infarction does not decrease, and in some cases increases mortality [1,2]. Our data on high toxicity of ethmozine and ethacizin, as well as on the safety of β-adrenoblockers, amiodarone, and calcium antagonists (verapamil) agree with clinical observations.

Of particular interest are the data on safety of antioxidants and quaternidine, a new Russian-made class III antiarrhythmic drug [5]. It should be noted that only indirect correspondence of experimental and clinical data could be discussed in this case.

Therefore, the proposed method is simple, inexpensive, and adequate for assessing safety of potential antiarrhythmic agents. The correlation between clinical results of a long-term antiarrhythmic therapy in some category of cardiovascular patients and our data can be explained by the same basic pathogenetic mechanisms mediating stress and ischemic damage to the heart [4].

TABLE 1. Mortality of Stressed Animals during Repeated Injection of Test Drugs

Group	Number of dead animals	
	abs.	%
Without immobilization (n=20)	0	0
Immobilization (control, n=40)	12	30
+lidocaine, 10 mg/kg (n=40)	21	52.5*
+ethmozine, 2 mg/kg (n=40)	36	90*
+ethacizin, 0.5 mg/kg (n=40)	36	90*
+propranolol, 0.5 mg/kg (n=40)	19	47.5
+amiodarone, 5 mg/kg (n=24)	8	33
+quaternidine, 2 mg/kg (n=40)	16	40
+verapamil, 0.5 mg/kg (n=40)	16	40
+dimephosphon, 100 mg/kg (n=52)	16	33.9
+mexidol, 20 mg/kg (n=40)	14	35
+cytochrome-c, 5 mg/kg (n=40)	5	12.5

Note. *p<0.05 compared to the control.

TABLE 2. Comparison of Experimental Results with Published Clinical Data

Drug	Experimental data	Clinical observations
Encainide, flecainide, ethmozine	Ethmozine and ethacizin 3-fold increase mortality of stressed mice	Total mortality increases 2-3-fold in comparison with placebo [8,9]
Lidocaine	Mortality increases by 22.5%	Preventive administration increases mortality in patients with myocardial infarction [1,2]
Propranolol and other β-adrenoblockers	Propranolol does not increase mortality of test animals during long-term immobilization stress	In postinfarction patients total mortality and the rate of sudden death decrease by 23-26% and 28%, respectively [6]
Amiodarone	Amiodarone and quaternidine do not increase mortality of stressed mice	Total mortality decreases by 21.2%, while arrhythmia-caused mortality decreases by 49% [7,13]
Verapamil	No increase in mortality of immobilized (stressed) albino mice	Mortality of patients does not change [10,11,14]
Tocopherol acetate, β-carotene	Mexidol, dimephosphon, and cytochrome-c do not increase mortality of stressed mice	Incidence of nonfatal myocardial infarction decreases, but total mortality does not change [12,16]

REFERENCES

1. J. Alpert and G. Fransis, *Handbook of Coronary Care*, Moscow, (1994).
2. M. Woodley and A. Whelan, in: *Therapeutic Manual of Washington University* [Russian Translation], Moscow (1995), pp. 186-235.
3. M. S. Kushakovskii, *Cardiac Arrhythmias* [in Russian], St. Petersburg (1998).
4. F. Z. Meerson, *Pathogenesis and Prevention of Stress and Ischemic Damage to the Heart* [in Russian], Moscow (1984).
5. I. Ya. Moiseeva and Ya. V. Kostin, *Vestn. Aritmol.*, **15**, 173 (2000).
6. T. Buckingham, A. Volgman, and E. Wimer, *Pacing Clin. Electrophysiol.*, **14**, 1437-1439 (1994).
7. J. Cairns, S. Connolly, R. Roberts, *et al.*, *Lancet*, **349**, 675-682 (1997).
8. D. S. Echt, P. R. Liebson, L. B. Mitchel, *et al.*, *N. Engl. J. Med.*, **324**, 781-788 (1991).
9. The cardiac arrhythmia suppression trial II investigators: Effect of the Antiarrhythmic Agent Moricizine on Survival after Miocardial Infarction, *Ibid.*, **327**, 227-233 (1992).

10. C. D. Furberg, B. M. Psaly, and J. V. Meyer, *Circulation*, **92**, 326-331 (1995).
11. C. D. Furberg, M. Pahor, and B. M. Psaly, *Eur. Heart J.*, **17**, 1142-1147 (1996).
12. C. H. Hennekens, J. E. Buring, J. F. Manson, *et al.*, *N. Engl. J. Med.,* **334**, 1145-1149 (1996).
13. D. Julian, A. Camm, G. Frangin, *et al.*, *Lancet*, **349**, 667-674 (1997).
14. P. A. Poole-Wilson, *Eur. Heart J.*, **17**, 1131-1133 (1996).
15. B. M. Psaty, R. R. Heckbet, T. D. Koepsell, *et al.*, *JAMA*, **224**, 620-625 (1995).
16. N. G. Stephens, A. Parson, P. M. Schofield, *et al.*, *Lancet*, **347**, 781-786 (1996).