COMBINED ACTION OF ANTIARRHYTHMIC AGENTS

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One of the foremost trends in modern pharmacotherapy is the combined use of drugs, which takes advantage of the phenomenon of potentiation, and also allows simultaneous intervention on several different stages of a pathological process. However, analysis of the clinical data shows that combinations of antiarrhythmic agents are used comparatively infrequently, and their use is mainly empirical in character, for it does not rest on an adequate experimental basis [3, 8, 9, 11].

This paper describes the results of an experimental study of several combinations of antiarrhythmics, taking account of their different effects on transmembrane ionic currents. Since antiarrhythmics are effective against particular disturbances of the cardiac rhythm, our aim was to seek combinations of drugs for the correction of ventricular arrhythmias, complicating the course of experimental myocardial infarction (MI).

EXPERIMENTAL METHOD

Having regard to the aims of the investigation, the following drugs were used as test objects: a quaternary derivative of ajmalin (N-propylajmalin bromide — PAB), the local anesthetic trimecaine, quinidine, and the β-adrenoblocker propranolol. Tests were carried out on 121 dogs weighing 8-14 kg with ventricular arrhythmia in the late stage (after 1 day) of experimental MI, produced by ligating the descending branch of the left coronary artery by the method described previously [1]. Together with other advantages, this model of arrhythmia enables the duration of the antiarrhythmic effect of drugs to be determined objectively and compared. Antiarrhythmics and their combinations were given either enterally (via gastric tube) or intravenously.

In different series of experiments the effective dose of the drug giving an antiarrhythmic effect in all or most of the experimental animals, and also the subthreshold dose, not causing normalization of the disturbed cardiac rhythm, or exerting an antiarrhythmic action in only a very small number of cases, were determined. When combinations of drugs were compared, they were used only in subthreshold doses, in order to discover whether potentiation of the antiarrhythmic effect could be demonstrated.

EXPERIMENTAL RESULTS

The heart rate of the experimental animals 24 h after occlusion of the coronary artery varied between 170 and 240 beats/min, and 87 ± 4% of contractions were ectopic in origin (polytopic ventricular extrasystoles).

It will be clear from Table 1 that subthreshold doses with no antiarrhythmic effect, or abolishing arrhythmia only in individual cases, when given enterally, amounted to 2 mg/kg for PAB, 50 mg/kg for trimecaine, and 2 mg/kg for propranolol, whereas by intravenous injection they were 10 mg/kg for quinidine and 10 mg/kg for trimecaine.

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TABLE 1. Antiarrhythmic Action of Single Drugs and Their Combinations against Ventricular Arrhythmia in Dogs in the Late Stage of Experimental MI

Drug or combination of drugs	Mode of administration	Dose, mg/kg	Number of animals			Time, min	
			in experiment	with CAAE		onset of CAAE	duration of CAAE
				absolute	%		
PAB	Enterally	4	7	4	57	45±4	469—89
	»	2	7	—	—	—	—
Quinidine	Intravenously	10	6	3	50	3—5	8±2
Trimecaine	»	15	10	7	70	2—3	6±1
	»	10	10	4	40	2—3	3—5
	Enterally	120	10	10	100	38±12	74±8
	»	75	6	3	50	50±17	30±6
	»	50	7	1	14	20	50
Propranolol	Intravenously	1,5	9	—	—	—	—
	Enterally	2,0	8	—	—	—	—
PAB + trimecaine	»	2	9	6	66	52±10	228±35
	»	50					
PAB + trimecaine + atropine	»	2					
		50	9	7	78	59±10	216±46
		0,2					
PAB + propranolol	»	2					
		2	6	4	67	64±14	198±21
Quinidine + trimecaine	Intravenously	10					
	»	10	17	15	88	2—3	106±22

Legend. CAAE) Complete antiarrhythmic effect (restoration of stable sinus rhythm).

The results of the experimental study of antiarrhythmic combinations show (Table 1) that a combination of PAB and trimecaine, in subthreshold doses of each, causes clear potentiation of the antiarrhythmic effect: a stable sinus rhythm was restored in six of nine dogs with ventricular arrhythmia; the complete antiarrhythmic effect lasted 228 ± 35 min. In the remaining three animals the ectopic discharge frequency was lowered by more than 50%. In another series of experiments, atropine was added to this combination to weaken inhibitory vagal influences on automatism of the sinus node. Abolition of ventricular arrhythmia and restoration of sinus rhythm were observed in seven of the nine experimental animals, i.e., in both series of experiments virtually identical potentiation of the action of the antiarrhythmics was observed when administered as a combination.

The results of a study of a combination of PAB and propranolol are particularly interesting, since this β-adrenoblocker by itself, when given intravenously or enterally, was ineffective on this model of arrhythmia [2]. However, with a combination of PAB in a subthreshold dose and of propranolol, given enterally, stable restoration of sinus rhythm was observed after 64 ± 14 min in four of the six experimental animals, and it lasted for 188 ± 21 min. In the remaining two animals, the ectopic firing was weakened by 37-69%.

Potentiation of the antiarrhythmic effect and its considerable prolongation also were observed after the combined intravenous injection of quinidine and trimecaine. In the case of experimental monotherapy, both drugs abolished ventricular arrhythmia and restored sinus rhythm in 40-50% of experimental animals; the antiarrhythmic effect, however, lasted for only a few minutes. With a combination of quinidine and trimecaine, used in the same doses, a complete antiarrhythmic effect was observed in 15 of the 17 experimental animals and, what is particularly striking, the restored sinus rhythm persisted for 106 ± 29 min ($p < 0.05$).

Thus a combination of drugs belonging to different classes of antiarrhythmics [12], for example, a combination of PAB (class IA) and trimecaine (class IB) or PAB and propranolol (class II), very considerably increases antiarrhythmic activity, whereas a combination of quinidine (class IA) and trimecaine potentiates and prolongs the antiarrhythmic effect.

These results were obtained on a model of ventricular arrhythmia in dogs in the late stage of experimental MI which, in the modern view [4, 5], is the result of ischemic changes in ionic currents, including an increase in the outward K^+-current, a decrease of the fast inward Na^+-current and the slow inward Na^+,Ca^{++}-current [10], and also a disturbance of function of the Na^+,K^+-pump, as a result of which foci of ectopic impulse formation arise in the Purkinje fibers and the conditions are created for reentry of the excitation wave [4, 5, 9].

The high efficacy of certain local anesthetics, possessing antiarrhythmic activity (class IB antiarrhythmics) on this model of arrhythmias is due, it has been suggested, to blockade of the fast Na^+-current [6], entering the cardiomyocytes of the boundary zone and of the intact myocardium and leading to reduction of electrophysiological dispersion of the heart muscle arising as a result of MI [4, 5].

The class IA antiarrhythmics which, besides delaying the slow Na^+,Ca^{++}-current (slow diastolic depolarization) and blockade of the inward fast Na^+-current, evidently also act in a similar manner, and inhibit the outward K^+-current from the cardiomyocytes [12], which impairs the dromotropic function of the myocardium and, in turn, promotes recovery of its functional homogeneity, extinguishes foci of heterotopic impulse formation, and interrupts circulation of the excitation wave (reentry).

The ineffectiveness of monotherapy of ventricular arrhythmia in the late stage of experimental MI with β-adrenoblockers is evidently attributable to their weak effect (in therapeutic doses) on the transmembrane ionic current in the cardiomyocytes [7, 13].

However, as our own experimental results show, a combination of antiarrhytmics differing in their mechanism of action significantly potentiates their antiarrhythmic action, possibly because the conditions are created for simultaneous inhibition of automatism of the ectopic sources of impulse formation and inhibition of reentry of the excitation wave, thus endowing the combinations of drugs with a wider range and more universal manifestation of their antiarrhythmic action.

The results can evidently be used as experimental justification for a rational combination of antiarrhythmics in clinical practice.

LITERATURE CITED

1. É. I. Gendenshtein and Ya. V. Kostin, Kardiologiya, No. 1, 128 (1976).
2. É. I. Gendenshtein, Ya. V. Kostin, and N. D. Volkova, Kardiologiya, No. 4, 116 (1977).
3. V. É. Oleinikov, I. P. Tatarchenko, and G. G. Zhivotovskaya, Kardiologiya, No. 9, 118 (1985).
4. V. I. Porotikov, A. V. Lazarev, and G. A. Glezer, Usp. Fiziol. Nauk, No. 3, 42 (1984).
5. M. E. Raiskina and B. N. Fel'd, Usp. Fiziol. Nauk, No. 3, 108 (1984).
6. L. V. Rozenshtraukh, E. P. Anyukhovskii, and G. G. Beloshapko, Byull. Éksp. Biol. Med., No. 1, 38 (1981).
7. I. B. Simon, V. P. Vvedenskii, I. I. Levshina, et al., Khim.-Farm. Zh., No. 3, 7 (1974).
8. L. Tomov and I. Tomov, Disturbances of the Cardiac Rhythm [in Russian], Sofia, Bulgaria (1979).
9. Z. I. Januškevičius, J. J. Bredekis, A. J. Lukoševičiute, et al., Disturbances of Rhythm and Conduction of the Heart [in Russian], Moscow (1984).
10. E. Coraboeuf, E. Deroubaix, and G. Horter, Circulat. Res., **36**, No. 5, Suppl. 1, 92 (1976).
11. D. J. Ross, D. I. Cre, D. L. Keefe, et al., Circulation, **66**, No. 6, 1205 (1982).
12. E. M. Vaughan Williams, J. Clin. Pharmacol., **24**, No. 4, 129 (1984).
13. A. L. Wit, B. F. Hoffman, and M. R. Rosen, Amer. Heart J., **90**, No. 6, 795 (1975).