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TROPAPHEN IN THE EXPERIMENTAL PHARMACOTHERAPY OF COR PULMONALE

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Peripheral vasodilators (PV) are nowadays widely used in clinical practice to treat heart failure because of their ability to improve cardiac activity indirectly through a change in tone and filling of the peripheral vessels and reduction of the pre-load and/or post-load on the heart. Reports of the use of PV with different mechanisms of action, including myotropic agents, calcium antagonists, and inhibitors of angiotensin-converting enzyme, in heart failure have been published [4, 9, 15]. The role of α-adrenoblockers (α-AB) in this aspect is unclear and calls for intensive study.

The aim of this investigation was to study the effect of the unselective α-AB tropaphen* on the cardio- and hemodynamics in a form of heart failure refractory to glycoside therapy, namely experimental cor pulmonale (CP), associated with chronic nonspecific lung diseases (CNLD).

EXPERIMENTAL METHOD

Experiments were carried out on 36 mongrel dogs of both sexes weighing 16-25 kg. The experiment consisted of three series: I) control animals; II) animals with a model of CP due to pulmonary hypertension (PHT), associa-

*Tropine ester of β-acetoxyphenyl-α-phenylpropionic acid.

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TABLE 1. Effect of Tropaphen (3 mg/kg) on Parameters of Cardiohemodynamics of Dogs with Cor Pulmonale

	Parameter	Control (n = 7)	CP (n = 7)	CP + tropaphen (n = 10-11)
Right ventricle	Maximal pressure, kPa	3.1±0.24	3.41±0.19	2.64±0.13**
	Developed pressure, kPa	1.7±0.13	2.4±0.16*	1.6±0.07**
	dp/dt max, kPa/sec	61.6±5.1	43.1±7.2*	63.2±6.5
	-dp/dt max, kPa/sec	43.7±3.5	36.0±4.5	41.6±3.6
	IC, sec^{-1}	37.5±2.5	17.5±2.1	39.96±4.6**
	IR, sec^{-1}	26.6±1.4	14.96±1.3*	26.1±2.1**
	DOLV	0.18±0.01	0.23±0.02*	0.17±0.01**
Left ventricle	Maximal pressure, kPa	17.1±0.65	16.3±1.04	17.2±0.99
	Developed pressure, kPa	8.8±0.47	11.7±0.81*	9.6±0.64
	dp/dt max, kPa/sec	283±25	227±22	305±30
	-dp/dt max, kPa/sec	226±19	188±13	266±28**
	IC, sec^{-1}	32.6±2.6	19.7±1.95*	32.1±3.2**
	IR, sec^{-1}	26.0±2.0	16.1±0.75*	28.2±2.8**

Legend. Here and in Table 2, significant differences ($p < 0.05$) indicated by asterisks: *) from control, **) from CP group.

TABLE 2. Effect of Tropaphen (3 mg/kg) on Work of the Heart and Systemic Hemodynamics in Dogs with Cor Pulmonale

Parameter	Control (n = 9–18)	CP (n = 7)	CP + tropaphen (n = 9-11)
CO, liters/min	1.98±0.24	1.54±0.14	3.64±0.37**
SV, liters	0.013±0.001	0.01±0.001	0.021±0.002**
Absolute cardiac output, liters/sec	0.033±0.004	0.026±0.002	0.061±0.006**
WILV, $N/min/m^2$	44.2±6.0	32.6±3.3	64.8±4.5**
TPR, kPa·sec/liter	451.1±35.5	596.5±98	259.3±28.5**
PR, kPa·sec/liter	37.9±4.8	78.6±10.0*	25.8±2.5**
PAR, kPa·sec/liter	43.2±6.3	78.2±12.1*	24.4±1.4**
Systemic BP, kPa	15.6±0.77	15.0±0.75	14.6±0.64
Pressure in pulmonary artery			
systolic, kPa	1.83±0.07	2.59±0.11*	2.09±0.09**
diastolic, kPa	0.95±0.11	1.32±0.12*	1.32±0.13
pulse, kPa	0.89±0.08	1.25±0.15*	0.77±0.11**
Central venous pressure, kPa	0.24±0.05	0.45±0.13	0.79±0.11
Heart rate, min^{-1}	162±8	157±8	179±7

ted with CNLD; III) animals with CP, receiving tropaphen. PHT and CP were produced over a period of 6 months by a method developed in the writers' laboratory (Authors' Certificates Nos. 826401 and 875449), consisting of repeated microembolization of the pulmonary arterioles with a suspension of hens' erythrocytes. Pharmacotherapy began 5 months after creation of the model of the pathological process. Tropaphen (Ministry of the Medical Industry of Russia) was injected in a dose equal to ED_{30} of the hypotensive effect (3 mg/kg), intramuscularly twice a day for 25 days. The state of the dogs hemodynamics was assessed in an acute experiment involving catheterization of the chambers of the heart and the great vessels and by the thermodilution method [2]. All experiments were conducted under hexobarbital anesthesia with premedication. Analysis of variance was used for statistical evaluation of the results.

EXPERIMENTAL RESULTS

After 6 months the experimental dogs with the model of CP exhibited PHT, an increase in the degree of overloading of the right ventricle (DOLV), depression of contractility and of the relaxation properties of the myocardium of both ventricles, and weakening of the pumping function of the heart (Tables 1 and 2).

The course of tropaphen was accompanied by stimulation of cardiac activity, more especially of the myocardium of the right ventricle. For instance, the indices of contractility (IC) and relaxation (IR) of the right ventricle rose by 128 and 74%, and of the left ventricle by 63 and 75% respectively, compared with the CP group, due to an increase in dp/dt and a decrease in the pressure developed by the right (by 33%) and, to a lesser degree, by the left (by 18%) ventricles.

The force of contraction of the right ventricle, which is reflected in the maximal pressure in the ventricle, and DOLV fell by 23 and 26% respectively, due to the vasodilator effect of trophaphen in the pulmonary circulation, where a significant fall of systolic pressure was recorded in the pulmonary artery almost to the control values (by 19%), together with a reduction of two-thirds of the total pulmonary (PR) and pulmonary arterial resistance (PAR). The pulmonary capillary and central venous pressure remained virtually unchanged.

Observations relating to the state of the central hemodynamics of the dogs with CP after pharmacotherapy with tropaphen are noteworthy A significant increase was found in cardiac output (CO) compared with CP (by 136%) due to an increase in the stroke volume (SV, by 110%) and a tendency toward tachycardia. The working (WILV) and working stroke (WSILV) indices of the left ventricle also were increased by 2 and 1.6 times respectively, and exceeded the control levels. The total peripheral resistance (TPR) was reduced by 57%, but the systemic arterial pressure (BP) did not fall in this case because of the increase in cardiac ejection. The residual central blood volume (RCBV) was unchanged during the experiment.

On the basis of analysis of these findings and their comparison with information in the literature [8, 11, 14] it can be postulated that one of the most probable mechanisms of the cardiotonic action of tropaphen in CP is a change in the response of the heart to loading and an indirect β-adrenomimetic action of the drug. In support of this latter suggestion there are the results of experiments [5] with preliminary blockade of β-adrenoreceptors, confirming their involvement in the myocardial stimulation arising under conditions of α-adrenergic blockade. The vasodilator action of tropaphenin this pathology is probably attributable to three factors: blockade of vascular α-adrenoreceptors, a direct myotropic action, and the ability of the drug to abolish pressor effects of biologically active substances on vessels of the pulmonary circulation [7, 12, 13]. Possibly it is these pharmacological properties of the drug that led to partial abolition of pulmonary hypertension, despite the considerable venous return of blood to the heart.

The results are thus evidence of a positive effect of tropaphen in CP, including an increase in the kinetic parameters of the heart, strengthening of its pumping function, abolition of pulmonary hypertension, and prevention of overloading of the right ventricle, and maintenance of stable values of the systemic BP and heart rate, and they provide a solid experimental indication for the use of tropaphen in the early stage of CP associated with CNLD, now and in the future.

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