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Prooxidant Effects of Nitrofurantoin

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We studied the possibility of using prooxidant effects of nitrofurantoin (furadonin) for stimulation of the natural antioxidant systems for preventing myocardial damage after coronary occlusion. A pronounced cardioprotective effect of the drug was observed.

Key Words: *5-nitrofuranes; nitrofurantoin; toxicity; lipid peroxidation; cardioprotective effect*

There are numerous reports on prooxidant, cytotoxic, and mutagenic effects of 5-nitrofuran derivatives. These effects are due to specific features of the cyclically repeated redox potential of these compounds [2,3].

Here we evaluated the possibility of using prooxidant effects of 5-nitrofuran compounds for stimulation of natural antioxidant systems via the feedback mechanism for prevention of pathological conditions associated with activation of lipid peroxidation and myocardial damage (ischemic and intact areas) in myocardial infarction.

MATERIALS AND METHODS

Therapeutic and supertherapeutic (with correction for metabolic processes), fractionated and long-term prooxidant effects of nitrofurantoin (furadonin) were studied on rats. The drug was given in doses of 30 and 300 mg/kg (1 and 10% LD_{50}, respectively) orally once a day for 30 days before myocardial infarction modeling.

Wistar male rats were divided into weight-matched groups. Since the dosage of nitrofurantoin was nonstandard, direct analysis of cardio- and hemodynamic parameters was supplemented by load tests.

We evaluated myocardial function the incidence and severity of early occlusion-induced arrhythmias during the acute period of infarction (the first 20 min). The intensity of lipid peroxidation (LPO) was evaluated by the concentrations malonic dialdehyde (MDA) and diene conjugates. Systemic organization of mechanisms of adaptation to prooxidant effect and "structural trace" was studied by comparing intermodal parameters (left-ventricular pressure after 25-sec aorta clamping, maximum left ventricular pressure during adrenoreactivity test, cardiomyocyte diameter, and MDA concentration) expressed in dimensionless arbitrary units [1].

The following parameters were used for characterizing antiarrhythmic effects of preventive 5-nitrofuran treatment: incidence, latency, duration, and type of arrhythmias, and animal mortality. ECG was recorded for 20 min after ligation of the coronary artery.

The effect of nitrofurantoin on LPO processes during experimental coronary occlusion was studied on 3 groups of animals: intact, controls (day 2 of myocardial infarction), and experimental (day 2 of myocardial infarction after preventive 30-day treatment with nitrofurantoin in a dose of 300 mg/day).

The intensity of LPO was evaluated by biochemical analysis of left-ventricular blood plasma on day 2 after myocardial infarction. The concentrations of primary and secondary LPO products (diene conjugates, ketodienes, and MDA), and final LPO products (complex bases) and total antioxidant activity of the plasma were measured.

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RESULTS

Long-term (30 days) preventive treatment with nitrofurantoin significantly and dose-dependently reduced the duration of arrhythmia, prolonged its latency and decreased animal mortality. Preventive treatment with higher doses of nitrofurantoin decreased the incidence of fatal fibrillations and significantly decreased animal mortality (to 10% *vs.* 60% in the control group, $p<0.05$). Treatment with lower doses also decreased mortality (to 20%), but the duration of arrhythmia (624±48 sec) did not significantly differ from the control (777±44 sec).

On day 2 of infarction the necrotic zone (planimetrically measured) was less extensive in rats receiving the higher dose of nitrofurantoin compared to controls (33.4±2.1 and 42.1±1.9%, respectively).

Comparison of the infarction zones in different areas of the heart showed that their size increased from the heart base to its apex in both the control and experimental groups. This can be explained by increased area of myocardial blood supply via the anterior descending branch of the left coronary artery and hence, a larger area of ischemia as a result of its occlusion.

The effect of the lower dose of nitrofurantoin on the size of necrotic zone after acute coronary occlusion was negligible.

Experimental myocardial infarction led to a significant decrease in hemodynamic parameters, except heart rate, which decreased insignificantly. Pretreatment with nitrofurantoin in the higher dose had a clear-cut cardioprotective effect and prevented a decrease of left-ventricular pressure. On the other hand, the velocity parameters did not differ from those in the control group. Treatment with the lower doses had no cardioprotective effect on the initial hemodynamic parameters.

Load tests were carried out in order to evaluate the prooxidant effect on cardiohemodynamic parameters more accurately.

Volume load in the absence of pronounced disorders of pumping function was characterized by a transient biphasic reaction of the left-ventricular pressure: this parameter sharply increased in response to bolus injection (phase 1), then decreased, presumably, due to vagal reflex (phase 2), and then a trace hypervolemic effect was observed (phase 3). The intensity of the latter effect depended on the initial volume of circulating blood, degree of blood loss, *etc.*

Adrenoreactivity test (10^{-6} M epinephrine hydrochloride, 0.1 ml/100 g, intravenously) produced a more pronounced positive inotropic reaction: left-ventricular pressure, rates of left-ventricular pressure increase and decrease, and intensity of functioning attained 162.9±4.7 mm Hg, 11,002±375 and 6749±161 mm Hg/sec and 61,211±2899 arb. units, respectively.

The resistance test induced a biphasic reaction of the heart. During the first few seconds the left-ventricular pressure sharply increased and attained 198±4.6 mm Hg by the 5th sec of occlusion (control group). It should be noted that overfilling of the left ventricle caused bradycardia. Phase 2 was characterized by gradual decrease in the inotropic response. Systolic tension decreased by the 25th sec, while bradycardia became more pronounced. In intact animals the increase in the end-diastolic pressure (EDP) by the 25th sec of the test did not surpass 12-13 mm Hg, which indicates that the relaxation mechanisms remained more or less intact.

Acute hypoxia modeled by discontinuation of artificial ventilation under conditions of open chest caused a 30-50% decrease of heart rate during the 1st min of hypoxia. Visually the heart increased in size and looked plethoric. By the 3rd min of hypoxia the heart rate decreased to 40-50 bpm and some animals developed acute left-ventricular insufficiency (discharges from the tracheostomic tube).

Resumption of artificial ventilation restored adequate cardiac function with a short-term (1-1.5 min) posthypoxic positive inotropic effect. The maximum increase in heart contractility during reoxygenation was taken as the value of posthypoxic myocardial reactivity. Parameters of myocardial contractility decreased by the end of the 5th min of reoxygenation.

Experimental acute myocardial infarction (day 2) markedly changed the parameters of load tests in narcotized rats. In control animals volume load caused an almost 2-fold lower increase in the intensity of heart functioning in comparison with intact animals. Heart adrenoreactivity also markedly decreased. The rise of the left-ventricular pressure was 42.5±3.1 mm Hg *vs.* 63.0±3.9 mm Hg in intact animals.

The pressure load (clamping of the aorta) also caused a less pronounced increase in the left-ventricular pressure and intensity of heart functioning. The most drastic changes were observed in EDP response. By the 15th sec of the test EDP increased to 51.2±3.4 mm Hg (this increase was paralleled by the development of bradycardia) and remained at this level until the end of the test, while in intact animals this parameter did not surpassed 15-18 mm Hg.

Preventive treatment with nitrofurantoin in a dose of 300 mg/kg completely prevented the reduction of the left-ventricular pressure and heart rate during coronary occlusion. The reaction of contractility to volume loading was similar to that in intact animals.

Adrenoreactivity, resistance (sec 5 and 25), and reoxygenation tests, despite lower left-ventricular pressure, rates of left-ventricular pressure increase and

decrease, and intensity of structure functioning showed cardioprotective effect of the treatment in comparison with the corresponding values in intact animals. The effect manifested in higher myocardial contractility compared to that in control animals or in rats treated with nitrofurantoin in low doses. The dynamics of EDP was the most demonstrative in this respect. Nitrofurantoin in the higher dose prevented the rise of EDP (more than 2-fold) during the test.

Nitrofurantoin treatment (300 mg/kg) produced a pronounced antioxidant effect. It prevented accumulation of diene conjugates and MDA. The concentrations of Schiff bases and total antioxidant activity of the plasma increased to 0.25±0.01 and 29.88±2.82, respectively, in comparison with intact animals (0.16± 0.03 and 16.99±0.48) and controls (0.21±0.01 and 14.68±0.05). This suggests that prevention of accumulation of primary LPO products is paralleled by an increase in total plasma antioxidant activity and confirms the hypothesis on realization of the cardioprotective effect of preventive nitrofurantoin treatment via a feedback mechanism at the expense of activation of natural antioxidant systems.

Hence, the hypothesis on the possibility of using prooxidant effects of 5-nitrofuranes was confirmed in experiments with preventive oral treatment with nitrofurantoin in a dose of 300 mg/kg. This treatment protected the heart from damage caused by acute coronary occlusion (myocardial infarction).

The cardioprotective effect of nitrofurantoin manifested in reduced animal mortality, reduced size of necrotic zone, and prevention of contractility disorders during load tests. Of particular importance is prevention of accumulation of primary and secondary LPO products (diene conjugates and MDA), increase in the concentrations of LPO end-products (Schiff bases), and activation of antioxidant defense. This fact confirms the hypothesis on the realization of the cardioprotective effect of nitrofurantoin via the feedback mechanism, *i.e.* activation of the natural antioxidant systems.

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