EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Myocardial Contractility after *in Vitro* Treatment with Class III Antiarrhythmic Drug Nibentan

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Myocardial contractility was studied *in vitro* in response to treatment with class III antiarrhythmic drug Nibentan. The contractile response to Nibentan in increasing concentrations of 1.66, 2.5, and 3.5 mM was estimated on strips of animal myocardium and human right atrial auricle.

Key Words: *Nibentan; myocardial contractility*

Class III antiarrhythmic drugs are most effective in the therapy of atrial arrhythmias (fibrillation and flutter) [5,6]. A new antiarrhythmic drug Nibentan (Russia) belongs to this class of drugs. Antiarrhythmic activity of Nibentan is associated with lengthening of the action potential (AP) and increase in the atrial refractory period. Nibentan inhibits delayed rectifier potassium current in isolated rat cardiomyocytes, increases AP duration in rabbit atrial fibers, and lengthens the refractory period in dog atria and ventricles *in situ, i.e.* produces a negative chronotropic effect. It remains unknown whether Nibentan (as well as other class III drugs) possesses inotropic activity [1-3].

Here we studied the effect of Nibentan on myocardial contractility.

MATERIALS AND METHODS

Contractile activity of the myocardium was studied *in vitro* on myocardial strips from male Wistar rats (n=10, 200-300 g) and 10 myocardial strips from human right atrial auricle (length 2-3 mm, thickness 0.8-1.0 mm). Human right atrial auricle was surgically resected and utilized according to the standard and schedule of operation.

The contractile response to Nibentan in increasing concentrations of 1.66, 2.5, and 3.5 mM was estimated on a PowerLab device (ADInstruments) equipped with a MLT 050/D force transducer (ADInstruments).

The animals were narcotized with urethane. After thoracotomy the heart was rapidly removed and placed in a Petri dish with oxygenated working solution. Stimulation (10 mV, 6 pulses per min, pulse duration 5 msec) was applied using an ESL-2 stimulator. Myocardial strips were prepared. The preparation was fixed vertically between a force sensor and support point. Myocardial strips were embedded into individual reservoirs (25 ml). The working solution of 119.8 μmol/liter NaCl, 5.4 μmol/liter KCl, 1.8 μmol/liter $CaCl_2$, 1.05 μmol/liter $MgCl_2$, 0.42 μmol/liter $NaHPO_4$, 0.28 μmol/liter ascorbic acid, and 5.05 μmol/liter glucose (28°C) and carbogen (95% O_2 and 5% CO_2) were delivered through each reservoir. Basic and acid buffers (Trizma, Sigma) were added to maintain pH 7.3-7.4. The preparations were stimulated via platinum electrodes with specified frequency characteristics.

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The results were recorded on a personal computer (Chart 4.0 software). The test preparations were maintained in the reservoir over a running-in period of 40-60 min. During this period the optimal tension was applied to muscle strips. The optimal tension corresponds to the point of stretching when a superior exercise is followed by the decrease in muscle contractility. Basal contractility was recorded over 5 min after the running-in period. Muscle contractility was measured over 20 min after addition of Nibentan in any concentration into the working solution. Muscle preparations were washed 3 times with the working solution for 5 min after stimulation with Nibentan. Basal contractility of muscle strips was recorded for each concentration of Nibentan. The strength of contraction in response to treatment with Nibentan was expressed in percents of the baseline level. The results were analyzed by means of Statgraphics software. We calculated M, m, δ, and confidence interval p in test samples. The differences were significant at $p<0.05$.

RESULTS

We revealed an increase or decrease in the strength of contraction. Nibentan in a concentration of 1.66 mM produced a positive inotropic effect on all muscle strips (19.60±2.74%). A negative inotropic effect was revealed in 50% muscle strips (27.60± 2.49%). It should be emphasized that the negative inotropic effect was much more pronounced than the positive inotropic effect ($p<0.05$). Increasing the concentration of Nibentan to 3.5 mM was accompanied by a decrease in positive inotropic effect (9.60±2.05%), which became less pronounced compared to that observed in experiments with Nibentan in a concentration of 1.66 mM. Nibentan in concentrations of 2.5 and 3.5 mM produced a significant positive and negative inotropic effect (Fig. 1).

The positive inotropic effect exceeded the baseline level by 10.70±1.99% and was observed in 50% muscle strips treated with Nibentan in a concentration of 1.66 mM. Nibentan in this concentration produced a negative inotropic effect on all muscle strips (23.3±5.8%). A negative inotropic effect was less significant after administration of Nibentan in a concentration of 2.5 mM (23.10± 3.58%). The maximum negative inotropic effect was revealed in all muscle strips (30.90±4.77%). Increasing the concentration of Nibentan was accompanied by an increase in positive inotropic effect from 10.76 to 23.06%. Administration of Nibentan in a concentration of 3.5 mM most significantly decreased contraction strength in atrial strips (40.10±7.57%), but produced a less pronounced positive inotropic effect (12.1±2.5%, Fig. 2).

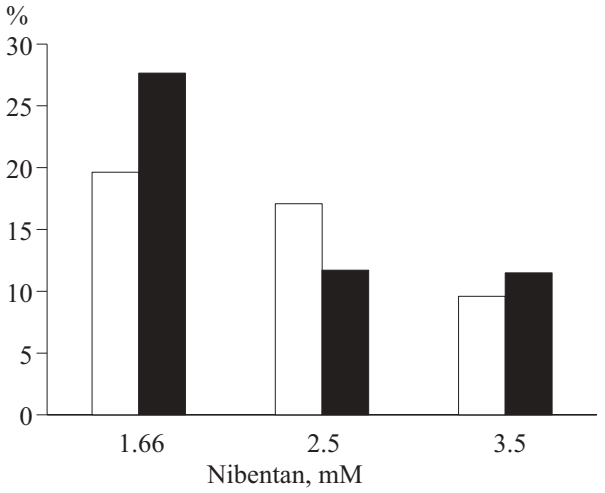

Fig. 1. Effect on Nibentan on myocardial contractility in rats. Here and in Fig. 2: light bars, positive inotropic effect; dark bars, negative inotropic effect.

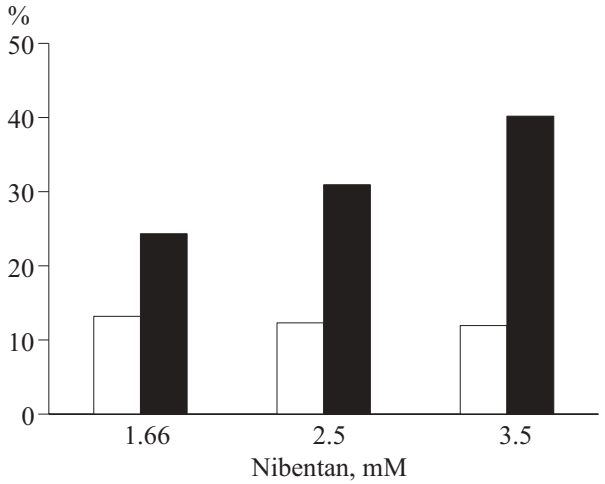

Fig. 2. Effect on Nibentan on myocardial contractility in a patient with coronary heart disease.

We showed for the first time that Nibentan dose-dependently modulates myocardial contractility *in vitro*. Increasing the concentration of Nibentan was accompanied by a decrease in the positive and negative inotropic effect. These changes reflect a decrease in the strength of contraction. Nibentan reduced the positive inotropic effect. Potentiation of the negative inotropic effect depended on the dose of Nibentan. Our findings open new indications for Nibentan in emergency cardiology.

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