EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Clinical and Experimental Study of Antiarrhythmic and Antianginal Effects of Quaternidine

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High antiarrhythmic activity of a new Russian antiarrhythmic drug quaternidine in ventricular arrhythmia was studied in 96 coronary patients by Holter monitoring, bicycle ergometry, and echocardiography. The drug had a positive impact on local kinetics in left-ventricular ischemic myocardium and some parameters of bicycle exercise test. The preparation possesses no arrhythmogenic effect. Experiments on 30 random-bred rats showed that the drug reduced the necrotic zone under conditions of experimental coronary occlusion. Experiments on 14 intact cats demonstrated that quaternidine had no effect on coronary bloodflow.

Key Words: *quaternidine; antiarrhythmic agent; antianginal effect; hemodynamics*

Treatment of cardiac arrhythmia is still a pressing problem in cardiology. Despite the necessity of treating ventricular extrasystole in myocardial infarction changed in recent years and prognostic value of these arrhythmias are now doubted, ventricular arrhythmias causing hemodynamic changes or subjectively poorly tolerated by the patients should be controlled [3,4]. The armory of antiarrhythmic drugs has notably widened in recent years. Many preparations with high antiarrhythmic activity do not contribute to reduction of total mortality due to their pronounced side effects (arrhythmogenic, negative inotropic, and dromotropic), which stimulates new search for potent antiarrhythmic drugs producing minimum side effects. In this context a new Russian drug quaternidine deserves special attention. The aim of the present study was to evaluate antiarrhythmic activity of quaternidine in coronary patients and patients with myocardial infarction, and to study the effects of this drug on coronary bloodflow and ischemic zones in experimental animals.

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MATERIALS AND METHODS

Clinical studies were carried out on 96 coronary patients (74 men and 22 women) aged 35-85 years (mean age 64.3±1.3 years). Subjects at a high risk of complications were excluded (heart failure functional class III-IV (NYHA), systolic arterial pressure below 90 mm Hg, sinus bradycardia, II-III degree sinoatrial and atrioventricular blocks, complete bundle branch block, chronic hepatorenal failure). No pregnant women participated in the study. Twenty-one patients had a history of myocardial infarction, 20 suffered from progressive angina pectoris, and 55 from effort angina functional classes I-III. All patients included in the study were treated by traditional protocols.

Quaternidine was injected intravenously to patients with progressive and stable angina in doses of 1.0-1.5 mg/kg (in 20 ml isotonic saline during 7-10 min in a supine position); to patients with a history of myocardial infarction it was injected in the same position in the same dose in 100 ml isotonic solution for 10-15 min. General status, behavior, respiration rate, diuresis, subjective sensations, arterial pressure, and

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heart rate were recorded before and 5, 10, 15, 30, and 60 min postinjection. Antiarrhythmic effect of quaternidine was evaluated in 66 patients by continuous 24-h Holter monitoring using Icar and Altair PC systems. In patients with myocardial infarction (n=21) heart rhythm was continuously monitored for several hours before and after the injection by Kardiokap monitor in a real-time mode in an intensive cardiology care ward. Bicycle ergometry (BEM) was carried out in 30 patients with a Tinturi bicycle ergometer. Antianginal activity of quaternidine was evaluated during graded exercise test in a sitting position with 60 rpm pedaling rate and initial load of 25-30 W; 12-lead ECG was recorded on a Mingograf-34 device (Siemens-Elema). BEM was repeated 60 min postinjection. The effect of quaternidine on local left-ventricular kinetics was studied in 9 patients by ultrasonic examination of the heart with a Combison 320-5 echocardiograph by evaluating local contraction [1]. Measurements were repeated 3 times in each segment and the arithmetic mean was calculated; a 13-segment division of the left ventricle was used.

Experiments were carried out on 30 albino random-bread rats (250-300 g) and 14 adult cats of both sexes (2.5-4.5 kg) narcotized with nembutal (50 mg/kg intraperitoneally). The cats were artificially ventilated. The size of ischemic and necrotic zones was evaluated 4 h after coronary occlusion [2]. Coronary bloodflow was studied by recording blood outflow from the coronary sinus. The effect of quaternidine on the function of ischemic myocardium was studied using a modified model of acute coronary failure [5].

Three control 5-min occlusions of the coronary vessel were followed by a 15-min reperfusion, after which quaternidine was infused (2.0 mg/kg intravenously) and reperfusion was repeated 3 times. Coronary occlusion was carried out 15, 35, and 45 min postinjection. The intensity of reversible ischemic damage was evaluated by elevation of the *ST* segment of epicardial ECG during short-term coronary occlusion.

The significance of differences was evaluated by Student's t test.

RESULTS

During preliminary ECG monitoring, ventricular extrasystoles of different gradations according to B. Lown were recorded, in 19 patients arrhythmia presented as a combination of ventricular extrasystoles and atrial fibrillation. Holter monitoring showed that quaternidine had a stable antiarrhythmic effect in 61 (92.4%) patients, in 42 (63.6%) patients the drug completely suppressed ectopic ventricular contractions. Antiarrhythmic effect of the drug depended on the form of coronary disease. In myocardial infarction, antiarrhythmic effect manifested 10-28 min postinjection (16.7±3.2 min). In 3 of 21 cases (14.3%) a biphasic antiarrhythmic effect was observed: ventricular extrasystoles disappeared immediately postinjection and returned after 3-5 min. A stable antiarrhythmic effect of quaternidine appeared after 15-25 min and persisted for 10 h 48 min (from 5 h 10 min to 16 h 30 min). Partial and complete antiarrhythmic effect persisted 11 h 56 min and 10 h 26 min, respectively. Quaternidine showed high antiarrhythmic activity in 20 patients (95.2%) with ventricular arrhythmias. Antiarrhythmic effect was complete in 16 (76.8%) patients (all extrasystoles disappeared) and partial in 4 (19.0%) (the number of extrasystoles decreased by 75-90% compared to the initial level). Only in 1 patient the drug was ineffective.

In progressive angina pectoris, antiarrhythmic effect was observed in 19 of 20 patients (95%), complete in 14 (70%); the differences from the myocardial infarction group were negligible. In stable effort angina, quaternidine produced a less potent antiarrhythmic effect: antiarrhythmic effect was observed in 22 (88%) cases, of them complete effect was noted only in 12 cases (48%). Hence, complete antiarrhythmic effect of quaternidine was 1.5 times higher in acute than in chronic coronary heart disease (p<0.05). Five patients reported side effects of quaternidine (transient numbness of the tip of the tongue and lips in 4 and giddiness in 1). Subjective improvement (less intensive heart pain or its cessation) was observed in 36 of 66 patients (54.4%). This effect was most pronounced in patients with progressive angina and myocardial infarction. Pain disappeared in 9 (36%) patients with stable angina, 15 (75%) with progressive angina, and 12 (57%) with myocardial infarction. This effect of the drug prompted additional study of its properties by the ultrasonic method (study of local kinetics) and paired BEM.

Paired BEM 60 min after a single injection showed less pronounced depression of *ST* segment (by 40%) in 2 patients and complete prevention of the segment depression in 1 patient. In 19 (63.3%) cases injection of quaternidine was associated with an increase of

TABLE 1. Paired BEB Test Values after Quaternidine Injection ($M\pm m$)

Parameter	Initial value	After quaternidine
Total exercise work, kgxm/min	3728±379	5167±427*
Exercise duration, min	6.4±0.4	7.9±0.5*
Threshold power, kgxm/min	730.0±15.2	815.0±13.5*
Double product, arb. units	241.9±10.6	248.6±10.2

Note. *p<0.05 compared to the initial value.

TABLE 2. Effect of Quaternidine (1 mg/kg) on the Size of Necrotic Zone in Rats 4 h after Coronary Occlusion ($M \pm m$)

Parameter	Control	Experiment
Ratio, %		
ischemic zone/total myocardium	34.0±2.6	34.0±3.6
necrotic zone/total myocardium	22±2	17.0±2.3
necrotic/ischemic zone	68.0±4.3	51.0±5.4*

Note. *$p<0.05$ compared to the control.

threshold power, exercise duration, and the total volume of work performed (Table 1). Subjectively it manifested in reduced pain syndrome or its absence.

Ultrasonic examination included only segments with sufficient visualization; all segments were divided into 2 groups. Group 1 included hypokinetic segments and group 2 included eu- and hyperkinetic segments. In group 1, quaternidine increased local contraction fraction by 1.6-16.7% of half of the small axis of left ventricle ellipsoid during 1-15 min postinjection (by 6.9% by the 5th min, on average, $p<0.05$). By the 30th min this value returned to the baseline. In group 2 an opposite trend was observed: a 2.8% decrease in the local contraction fraction during the first 15 min after the start of infusion, which also leveled by the 30th min.

Comparison of the results of ultrasonic examination and paired BEM suggests an antianginal effect of quaternidine. In order to verify the presence of this effect, we evaluated the influence of quaternidine on necrotic zone in acute myocardial ischemia. Quaternidine did not cause untoward changes in ischemic and necrotic zones. Ischemic zone in the control and after injection of quaternidine (1 mg/kg) was just a little more than 30% of the total bulk of the myocardium (Table 2). The size of necrotic zone was lower than in the control, but this difference was insignificant. The ratio of necrotic to ischemic zone after quaternidine treatment was significantly lower than in the control (Table 2).

In cats quaternidine in a dose of 2 mg/kg negligibly decreased the coronary blood flow velocity during the first 2-5 min (from 11.0±3.3 to 7.9±1.4 ml/min), by the 15th min this parameter was 9.6±2.1 ml/min, and after 20 min it returned to the initial level (all differences were negligible). In acute coronary failure quaternidine produced significant changes in *ST* segment on epicardial ECG.

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