A Comparative Study of the Effects of Dimebon, Obsidan, Finoptin, and Cordaron on the Functional State of Ischemic Focus and Size of Necrotic Zone in Experimental Myocardial Infarction

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Dimebon, an antihistamine agent, exerts a moderate antianginal effect, improving the function of ischemic focus in the myocardium and decreasing the necrotic zone in experimental myocardial infarction. Dimebon is less active than obsidan, finoptin (except for the size of the necrotic zone), and cordaron.

Key Words: *dimebon; obsidan; finoptin; cordaron; ischemia; myocardial infarction; treatment*

The H_1-receptor blocker dimebon exhibits antiarrhythmic activity in a wide dose range (0.1-10.8 mg/kg), being effective against cardiac rhythm disturbances of different origins, including those induced by experimental myocardial infarction [2].

At 5 and 7.5 mg/kg dimebon increases the rate of coronary blood flow and decreases oxygen consumption by the myocardium, creating an oxygen reserve in the heart in local acute myocardial ischemia.

In this study we compared the effects of dimebon with those of obsidan (propranolol), finoptin (verapamil), and cordaron (amiodarone) on the functional state of ischemic focus in the myocardium and on the size of the necrotic zone (NZ) in experimental myocardial infarction.

MATERIALS AND METHODS

Experiments were performed on 20 cats weighing 2.5-4.2 kg. The animals were anesthetized with Nembutal (40 mg/kg intraperitoneally), and local myocardial ischemia was induced by a 5-min clamping of the descending branch of the left coronary artery (DBLCA) in its middle third. The activities of the drugs were assessed by depression of the *ST* segment (ΣST) on the epicardial electrogram (EG) recorded from 6 sites of a heart surface [4,8]. The drugs were injected intravenously.

The effects of the drugs on the size of NZ in experimental myocardial infarction were studied on 40 cats weighing 2.8-4.2 kg. The animals were anesthetized with Nembutal (40 mg/kg intraperitoneally). Myocardial infarction was produced by occlusion of the DBLCA between the upper and middle third. The size of NZ was determined as described elsewhere [3]. The drugs were injected intravenously 30 min before and 120 min after ligation of DBLCA.

The results were statistically processed as described previously [1,7].

RESULTS

Depression of the *ST* segment was observed after administration of dimebon in a dose of 7.5 mg/kg. The greatest decrease in ΣST (40.3%) was recorded

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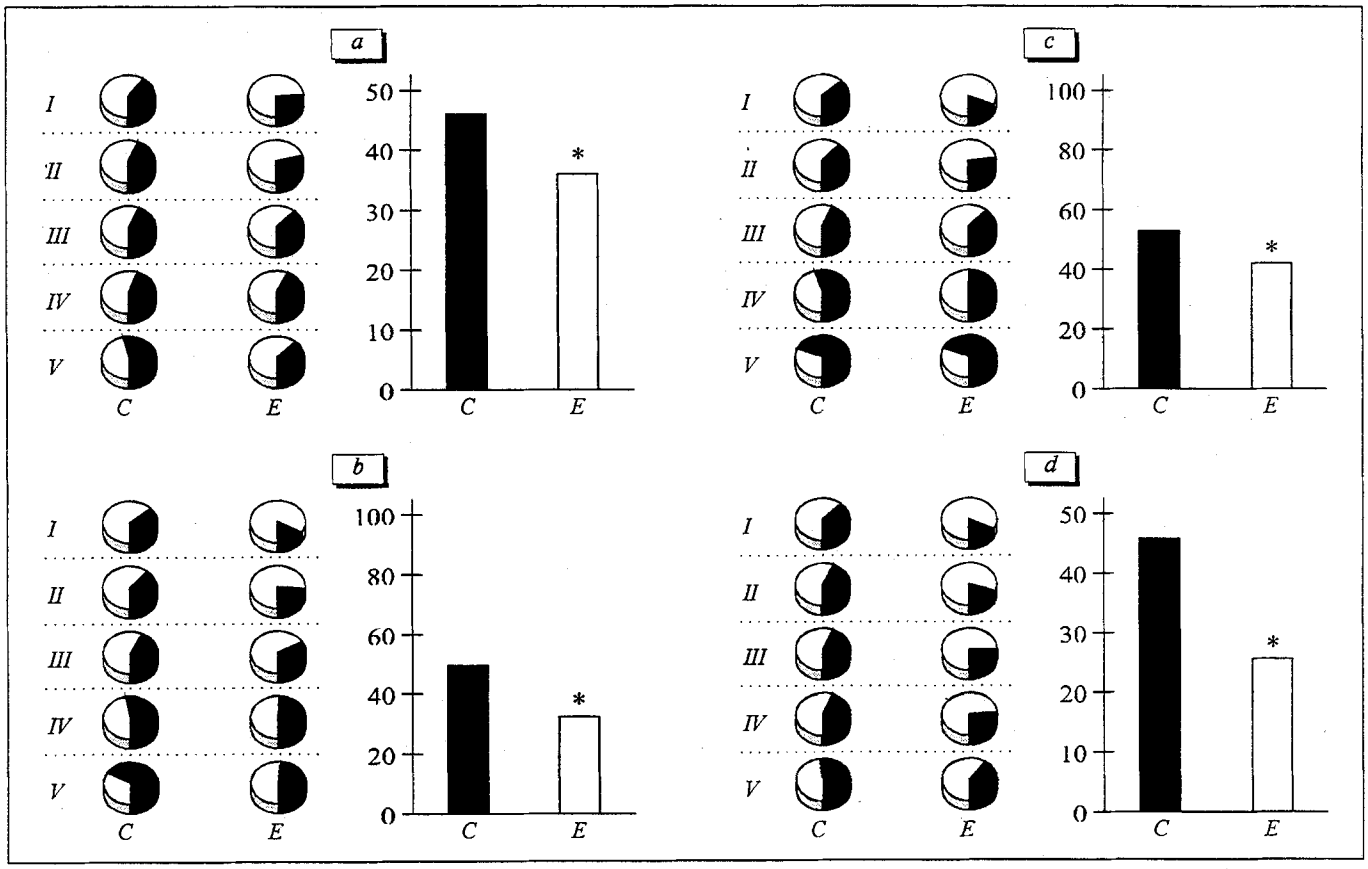

Fig. 1. Effects of dimebon (*a*), obsidan (*b*), finoptin (*c*), and cordaron (*d*) on the size of necrotic zone in cats with experimental myocardial infarction. Left: circle diagrams showing necrosis zone control (*C*) and experimental (*E*) animals. Dark area is the percent of necrotic zone of the section area. Right: necrotic is shown as percent of the total weight of the left ventricle in control (*C*) and experimental (*E*) animals. *Differences are statistically significant at $p<0.05$.

3 min after administration of dimebon on the first minute of DBLCA clamping. The effect lasted 20-30 min; the *ST* segment depression was noticed 1 min after DBLCA clamping and observed throughout the entire experimental period.

Obsidan (0.25 mg/kg) improved the functional state of ischemic focus. The most pronounced decrease in ΣST (48.1%) was observed 20 min after injection of the drug on the first minute of DBLCA occlusion. The effect lasted 40 min, the maximum depression of *ST* segment being recorded during the first minute of occlusion throughout the observation period.

With finoptin (0.25 mg/kg), the maximum decrease in ΣST (45.7%) was observed 3 min after its injection on the 30th sec of DBLCA clamping. The duration of the effect was 30-40 min.

Administration of cordaron (10 mg/kg) resulted in depression of the ΣST segment. The maximum (52.4%) depression was observed 3 min after injection on the third minute of occlusion. The drug effect lasted only 20 min.

These findings show that dimebon is inferior to obsidan, finoptin, and cordaron in its ability to improve the response of cat myocardium to ischemia. Since the height of the *ST* segment on epicardial EG reflects the severity of ischemic injury to the myocardium [9], which correlates with biochemical changes in the ischemic focus (depletion of macroergic phosphates, increased activity of creatine phosphokinase, and increased production of lactate [10,11]), it can be concluded that dimebon prevents the development of ischemic changes in the myocardium induced by occlusion of the DBLCA.

In cats with experimental myocardial infarction, the size of NZ decreased by 23.3% after two injections of 5 mg/kg dimebon (Fig. 1, *a*). Analysis of the cardioprotective effect of dimebon with the use of sections cut through different levels of the myocardium showed that a decrease in the size of NZ was more pronounced at the 1st and 2nd level (35 and 32.8%, respectively), than at the 5th, 3rd, and 4th level (28, 11.8, and 3.3%, respectively).

After administration of obsidan (0.25 mg/kg, two times), the size of NZ decreased by 30% (Fig. 1, *b*) in comparison with the control. The effect was more pronounced on myocardial sections of the 1st and

2nd levels (54.6 and 39.2%, respectively) that on sections cut at 5th, 3rd, and 4th level (27.1, 23.5, and 6.8%, respectively).

Two injections of finoptin in a dose of 0.25 mg/kg led to a 25.7% decrease in the size of NZ compared with the control (Fig. 1, *c*). The maximum cardioprotective effect was observed on the 1st level sections: the NZ was 52.1% smaller than in the control. The effect was less pronounced on sections cut through the 2nd, 3rd, and 4th levels: 29.6, 10.4, and 8.4%, respectively), being minimal (0.6%) at the 5th level.

Cordaron (10 mg/kg, two injections) reduced NZ by 46.8% (Fig. 1, *d*). The drug effect was pronounced on the sections cut at the 1st and 2nd levels (55.2 and 55.1% decrease, respectively, compared with the control) and became weaker at the 3rd, 4th, and 5th levels: 43.6, 39.6, and 21.6%, respectively.

Thus, the ability of dimebon to limit experimental myocardial infarction is close to that of finoptin and is lower than that of obsidan and cordaron. Our experiments showed a tendency toward an increase in the necrotic mass from the base of the heart to its apex both in control and experimental animals. This is explained by the fact that the area of myocardium supplied by the left coronary artery increases with its branching, and, consequently, the size of necrosis resulting from occlusion of this artery also increases. Interestingly, the maximum statistically significant decrease in the NZ area provided by all the studied drugs occurred at the 1st and 2nd levels of the myocardium, i.e., close to the site of DBLCA occlusion; while at the 3rd, 4th, and 5th levels (closer to the heart apex) the effects of these drugs were less pronounced. The infarction/peri-infarction zones ratio is different at different levels of the myocardium, increasing with the area supplied by the DBLCA [6]. The fact that a decrease in the NZ area is more pronounced at the 1st and 2nd levels than at the 3rd, 4th, and 5th levels suggests that the peri-infarction zone is better protected by the studied drugs.

The cardioprotective effect of dimebon may be associated with its antioxidant activity and stimulation of collateral circulation in the focus of myocardial ischemia, activation of antioxidant enzymes, and a decrease in the creatine phosphokinase activity and in lipid peroxidation. The ability of dimebon to neutralize the membranotropic effects of histamine may also contribute to its anti-ischemic activity.

Thus, dimebon elicits a moderate antianginal effect, improving the function of a myocardial ischemic focus and reducing NZ in experimental myocardial infarction. The drug is less active than obsidan, finoptin (except a decrease in the size of the necrotic zone), and cordaron.

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