EFFECT OF NONACHLAZINE AND OXYFEDRINE ON A FOCUS OF MYOCARDIAL ISCHEMIA

G. G. Chichkanov and A. K. Bogolepov

UDC 615.224.015.4:
616.127-005.4-092.9

Experiments on dogs, using the experimental model of angina pectoris developed by Szekeres et al. and modified by the writers, showed that nonachlazine in doses of 3 and 5 mg/kg reduce or even completely prevent the elevation of the ST segment on the epicardial ECG from a focus of myocardial ischemia. Oxyfedrine in doses of 0.05, 0.1, and 0.3 mg/kg had no such action. In doses of 0.1 and 0.3 mg/kg oxyfedrine worsened the epicardial ECG.

KEY WORDS: epicardial ECG; oxyfedrine; nonachlazine.

In recent years pharmacological agents capable of stimulating β-adrenergic receptors to a certain extent have been used with considerable success in the treatment of patients with ischemic heart disease. These agents include oxyfedrine and the new anti-anginal drug nonachlazine, synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR [1, 2, 4, 11]. Their effect on the total blood flow in the myocardium, tone of the coronary vessels, contractility of the heart muscle and cardiac activity has now been well studied experimentally. Yet the effect of drugs of this type on a focus of myocardial ischemia (on its blood supply and metabolism) remains unsettled. The investigation described below aims to fill the gap in this important region to a certain extent, not only from the theoretical, but more especially from the practical standpoint.

EXPERIMENTAL METHOD

The experimental model of angina pectoris developed by Szekeres et al. [12], was modified by the present writers. The principle of the method is as follows. Under general pentobarbital anesthesia (40 mg/kg, intravenously) and with artificial respiration, thoracotomy was performed in the fourth left intercostal space. By means of a special clamp the lumen of the left descending coronary artery was reduced and, at the same time, an artificial rhythm, 70 to 90 beats/min above the background level, was imposed on the heart. This was done by electrical stimulation of the right auricle through platinum electrodes (parameters of stimulation: 10 V, 1 msec). During stimulation for 3-5 min a focus of ischemia was formed in the myocardium and recorded in several epicardial leads of the ECG. The experiments were carried out so that neither the decrease in the lumen of the left descending coronary artery nor the imposition of the artificial rhythm caused any ischemic changes in the myocardium. Only the two factors together led to a marked rise in the ST segment in epicardial leads of the ECG, evidence of ischemia. By means of this model it was thus possible to study the effect of pharmacological agents on a focus of myocardial ischemia. Essentially this model is very similar to the physical exertion test on a bicycle ergometer, such as is widely used in clinical practice to assess the efficacy of anti-anginal drugs in patients with ischemic heart disease. In the present experiment the antianginal drugs were injected intravenously: nonachlazine in doses of 3 and 5 mg/kg, oxyfedrine in doses of 0.05, 0.1, and 0.3 mg/kg. Altogether 19 dogs were used in the experiments.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that nonachlazine, in doses of 3 and 5 mg/kg, considerably reduced or even completely prevented the appearance of ischemic changes on the epicardial ECG depending on the severity of the ischemia, which was reflected in the height of elevation of the ST segment. The effect of the drug in a dose

Laboratory of Pharmacology of the Cardiovascular System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 12, pp. 691-694, December, 1978. Original article submitted May 19, 1978.

 0007-4888/78/8612-1618$07.50

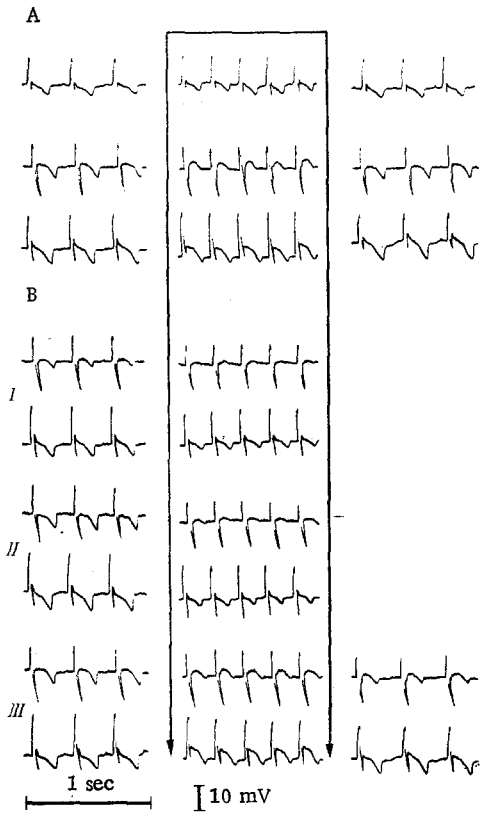

Fig. 1. Effect of nonachlazine on focus of myocardial ischemia. A) Before injection of nonachlazine. From top to bottom: area of myocardium in which stimulation caused no change in epicardial ECG; two areas where changes occurred during stimulation (elevation of ST segment); B) the same two areas 5 (I), 60 (II), and 90 (III) min after injection of nonachlazine in dose of 5 mg/kg. In A and B from left to right: Control, end of 5th min of stimulation, recovery after stimulation.

of 5 mg/kg was stronger. For instance, in 7 experiments in which the background elevation of the ST segment during stimulation at the third minute was 3.8 ± 0.5 mV, nonachlazine in a dose of 5 mg/kg in 6 experiments completely prevented the appearance of ischemic changes on the epicardial ECG, and only in one experiment reduced the elevation of the ST segment from 4 to 1.5 mV. The action of the drug continued for 30-90 min (Fig. 1). These results are in agreement with clinical observations showing that nonachlazine increases tolerance to physical exertion in patients with ischemic heart disease [6].

Oxyfedrine did not produce an effect similar to that of nonachlazine. On the contrary, in doses of 0.1 and 0.3 mg/kg it caused an even greater elevation of the ST segment in the epicardial leads of the ECG than in the control. For instance, in five experiments in which elevation of the ST segment at the third minute of stimulation was 2.8 ± 0.48 mV, oxyfedrine injected in a dose of 0.3 mg/kg increased the elevation of the ST segment to 5.2 ± 0.61 mV ($P < 0.05$) (Fig. 2). Furthermore, oxyfedrine, in doses of 0.1 and 0.3 mg/kg, caused tachycardia and frequently led to worsening of the epicardial ECG without imposition of an artificial rhythm on the heart.

In earlier experiments in which the coronary blood flow was recorded by an ultrasonic method the writers showed that nonachlazine in doses of 1 and 3 mg/kg has no significant effect on the volume velocity of the coronary blood flow in dogs. In a dose of 5 mg/kg nonachlazine increased the coronary blood flow only at the time of injection and during the next 2-3 min. The heart rate was reduced by the action of the drug. Later the coronary blood flow actually fell below its initial level. Oxyfedrine, in a dose of 0.3 mg/kg, increased the coronary blood flow to the same extent as nonachlazine. However, the effect of oxyfedrine lasted longer (20-30 min) and was accompanied by tachycardia [3]. If the data on the effect of the two drugs on the volume velocity of the coronary blood flow are compared with the data on their effect on an ischemic focus described above, it

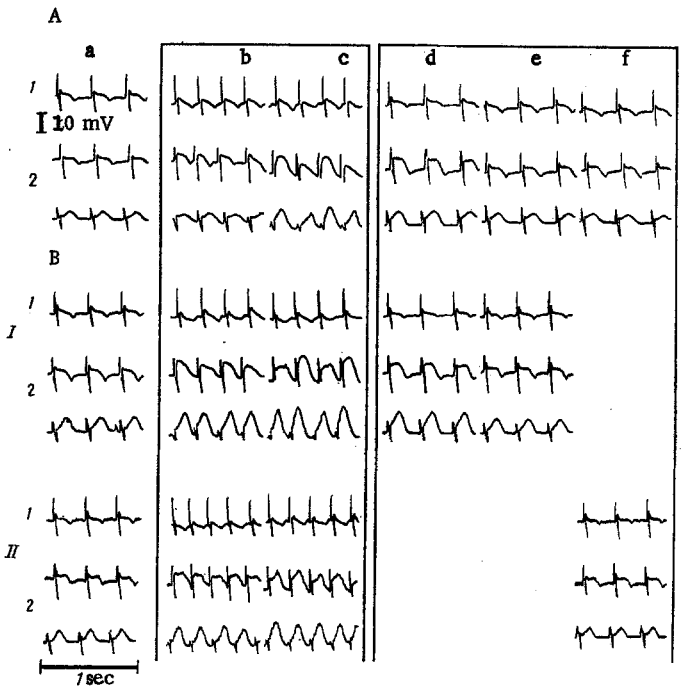

Fig. 2. Effect of oxyfedrine on focus of myocardial ischemia. A) Before injection of oxyfedrine; B) 5 (I) and 50 (II) min after injection of drug in dose of 0.1 mg/kg; in A and B, from top to bottom: 1) Area of myocardium in which stimulation caused no change in epicardial ECG; 2) area where changes occurred during stimulation (elevation of ST segment); a) control; b) end of first min of stimulation; c) end of third min of stimulation; d) first min after stimulation; e) seventh min after stimulation; f) tenth min after stimulation.

will be clear that there was no direct correlation between the total blood supply in the healthy heart and the state of the ischemic focus. The coronary blood flow was in fact increased for a long time under the influence of the drug, whereas the state of the focus of myocardial ischemia worsened, and vice versa. That is why in recent years when the effect of anti-anginal drugs on the coronary circulation has been studied investigators have begun to pay special attention to the effect of the drugs actually on the blood supply to the ischemic focus. Many drugs, while considerably increasing the volume velocity of the coronary blood flow in the heart, have been shown to reduce the blood supply to the ischemic focus [9, 10]. Furthermore Szekeres et al. [12], with their model of angina pectoris, have convincingly shown that the drug dipyridamole, although a strong coronary dilator, does not prevent elevation of the ST segment in the epicardial ECG. Meanwhile nitroglycerine and β-blockers give similar effects and considerably reduce the elevation of the ST segment.

Clear proof has now been obtained that elevation of the ST segment of the ECG is a characteristic sign of myocardial ischemia. Recent experimental investigations with epicardial electrocardiography, moreover, have shown a connection between the electrical changes in the myocardium and changes in the blood flow and tissue metabolism in the heart muscle. Clear correlation has been demonstrated between the amount of elevation of the ST segment on the epicardial ECG and the degree of reduction of the coronary blood flow, the intramyocardial pO_2, exhaustion of high-energy phosphates, and the fall in the creatine-phosphokinase level in the ischemic area of the myocardium [7, 8].

It can be concluded from the data given above that nonachlazine and oxyfedrine, while sharing the common property of stimulating β-adrenergic structures of the heart to some degree, differ in their effect on the blood supply and metabolism of a focus of myocardial ischemia. This conclusion is confirmed by results obtained previously in a study of the effect of two drugs on the oxygen uptake by the heart. Oxyfedrine, unlike nonachlazine and many anti-anginal drugs, although it increased the coronary blood flow rate, did not change, or actually reduced the oxyhemoglobin concentration in blood taken from the coronary sinus of the heart. This is evidence that oxyfedrine considerably increases the oxygen uptake by the heart [5].

LITERATURE CITED

1. V. I. Metelitsa, L. V. Chazova, R. A. Grigoryants, et al., in: New Therapeutic Possibilities in the Treatment of Ischemic Heart Disease with Special Attention to the Drug Ildamen (Oxyfedrine) (Symposium) [in Russian], Moscow (1976), pp. 55-66.
2. V. I. Metelitsa, L. V. Chazova, R. A. Grigoryants, et al., Ter. Arkh., No. 4, 44 (1977).
3. N. V. Kaverina, G. G. Chichkanov, V. B. Chumburidze, et al., Byull. Éksp. Biol. Med., No. 1, 34 (1977).
4. P. M. Savenkov, T. G. Nikolashchenko, D. D. Shcherbatkin, et al., in: New Therapeutic Possibilities in the Treatment of Ischemic Heart Disease with Special Attention to the Drug Ildamen (Oxyfedrine) (Symposium), [in Russian], Moscow (1976), pp. 89-94.
5. G. G. Chichkanov and V. B. Chumburidze, Farmakol. i Toksikol., No. 3, 302 (1977).
6. A. P. Yurenev, V. B. Chumburidze, and O. Yu. At'kov, Klin. Med., No. 5, 50 (1977).
7. J. Karlsson, G. H. Templeton, and J. T. Willerson, Circ. Res., 32, 725 (1973).
8. P. R. Maroko, J. K. Kjekshus, B. E. Sebel, et al., Circulation, 43, 67 (1973).
9. J. R. Parratt, Rev. Med., 16, 25 (1975).
10. J. R. Parratt, in: New Therapeutic Possibilities in the Treatment of Ischemic Heart Disease with Special Attention to the Drug Ildamen (Oxyfedrine) (Symposium) [in Russian], Moscow (1976), pp. 16-30.
11. W. Sternitzke, in: New Therapeutic Possiblities in the Treatment of Ischemic Heart Disease with Special Attention to the Drug Ildamen (Oxyfedrine) (Symposium), [in Russian], Moscow (1976), pp.67-78.
12. L. Szekeres, V. Csik, and E. Udvary, J. Pharmacol. Exp. Ther., 196, 15 (1976).

EFFECT OF INSULIN AND PREDNISOLONE ON TRANSPORT OF ORGANIC SUBSTANCES IN THE DOG KIDNEY

V. M. Bryukhanov and A. I. Nikitin

UDC 615.357.379+615.357.453].015.4:612.46

In experiments on dogs a single injection of insulin in a dose of 1 unit/kg body weight caused an increase in the maximal reabsorption of glucose and secretion of diodone and reduced the excretion of sodium without any change in glomerular filtration. These effects depend on the direct action of insulin, for when it was injected directly into one of the renal arteries its action was manifested only in the kidney on the side of infusion. Prednisolone had no significant effect on glucose and diodone transport when given as a single injection (3-4 mg/kg) or over a period of 10 days (1.5-2 mg/kg daily).

KEY WORDS: Insulin; prednisolone; glucose reabsorption; tubular secretion; excretion of sodium by the kidney.

Insulin and glucocorticoids are among the main regulators of carbohydrate metabolism. Nevertheless, their effect on glucose transport in the kidneys has been inadequately studied. In experimental animals and in man both a decrease [5, 6] and an increase [3, 4] in glucose reabsorption have been observed under the influence of insulin. The action of glucocorticoids on glucose transport has virtually not been studied.

EXPERIMENTAL METHOD

Acute experiments were carried out on 23 dogs. A solution containing 0.8% sodium chloride, 0.03% potassium chloride, 0.7% inulin, 25% glucose, and 2% diodone was injected at a constant rate intravenously into the animals. The technique of the experiments and method of determining the various substances were described previously [1]. In 11 experiments prednisolone was injected intravenously in a dose of 3-4 mg/kg and in 12 experiments insulin was injected into the left renal artery at the rate of 0.1 unit/min. The injection continued for 30-40 min.

Department of Pharmacology, Altai Medical Institute, Barnaul.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 12, pp. 694-697, December, 1978. Original article submitted May 19, 1978.

0007-4888/78/8612-1621$07.50