EFFECT OF PRELIMINARY PHARMACOTHERAPY ON THE COURSE OF ACUTE MYOCARDIAL ISCHEMIA IN DOGS

V. M. Koryukin and V. A. Pryanishnikov

UDC 616.127-005.4-36.11-091.8

In dogs with acute myocardial ischemia the most complete mobilization of glycogen and the most complete and effective utilization of its breakdown products are observed after preliminary treatment with izatin, and not of γ-hydroxybutyric acid (GHBA) and gutimin. Izatin potentiates the beneficial effect of GHBA on the energy metabolism of the myocardium.

KEY WORDS: myocardium; γ-hydroxybutyric acid; izatin; gutimin, carbohydrate metabolism.

Operations for revascularization of the myocardium are widely used at the present time in the combined treatment of patients with acute and chronic coronary insufficiency. A problem of considerable importance is that of the pharmacological preparation of the patients, with the aim of increasing the resistance of the myocardial tissues to ischemia [4, 8, 11]. This is also closely connected with the choice of anesthetic to be administered to these patients, for many anesthetics have an adverse effect on the myocardium [5, 7, 12]. As several workers have shown [3, 6, 13], besides its anesthetic properties, γ-hydroxybutyric acid (GHBA) possesses an antihypoxic effect on tissues, including the myocardium.

The object of the present investigation was to study the effect of GHBA alone and in conjunction with the antihypoxic drugs gutimin and izatin on the bioenergetics of the myocardium in dogs with acute experimental ischemia.

EXPERIMENTAL METHOD

Experiments were carried out on male mongrel dogs weighing 13-16 kg. An infarct of the myocardium was produced by ligation of the anterior coronary artery (CA) in its middle third. The antihypoxic drugs were given 30-40 min before mobilization of CA. The blood flow was restored 90 min later by removal of the ligature and the dogs were released from the experiment 90 min after recovery of the blood flow. The animals were divided into three groups. In group 1 gutimin (guanylthiourea) in conjunction with GHBA was used as the antihypoxic agent, in group 2 izatin, a derivative of α-dicarbonyl compounds, and GHBA were used. The antihypoxic agents were injected intraperitoneally in a dose of 150 mg/kg. Group 3 (control) consisted of animals in which ischemia developed against the background of general anesthesia with GHBA (1.5 g/kg). For preoperative preparation, hexobarbital (20 mg/kg, intramuscularly) was used, and for intravenous anesthesia a 1% solution of hexobarbital (30-40 ml) was injected.

In the course of the experiment the dynamics of the arterial pressure and the ECG were recorded, and the strength of the cardiac contractions was determined tensometrically, both in the zone of ischemia and in an intact zone, by the use of strain gauges of the Yu-12 type. For the histochemical control pieces of myocardium from the left ventricle of the animals before mobilization of CA, 90 min after the beginning of ischemia, and 90 min after restoration of the coronary blood flow (RCBF) were investigated. Pieces measuring 3 × 3 mm were taken from intact myocardium and from the zones of infarction, and frozen in liquid nitrogen. Glycogen was detected (by the McManus reaction) and activity of phosphorylase (after Lindberg and Palkama), lactate dehydrogenase (LD), succinate dehydrogenase (SD), mitochondrial and ctyoplasmic α-glycerophosphate dehydrogenase (α-GPM, α-GPC), and NADP-diaphorase (after Altman) was investigated in cryostat sections 10 μ thick. The cryostat section was stained with

Professorial Surgical Clinic, Department of Experimental Surgery, and Department of Morphology, Central Research Laboratory, I. P. Pavlov First Leningrad Medical Institute, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR F. G. Ublov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 5, pp. 429-432, May, 1979. Original article submitted April 18, 1978.

0007-4888/79/8705-0443$07.50

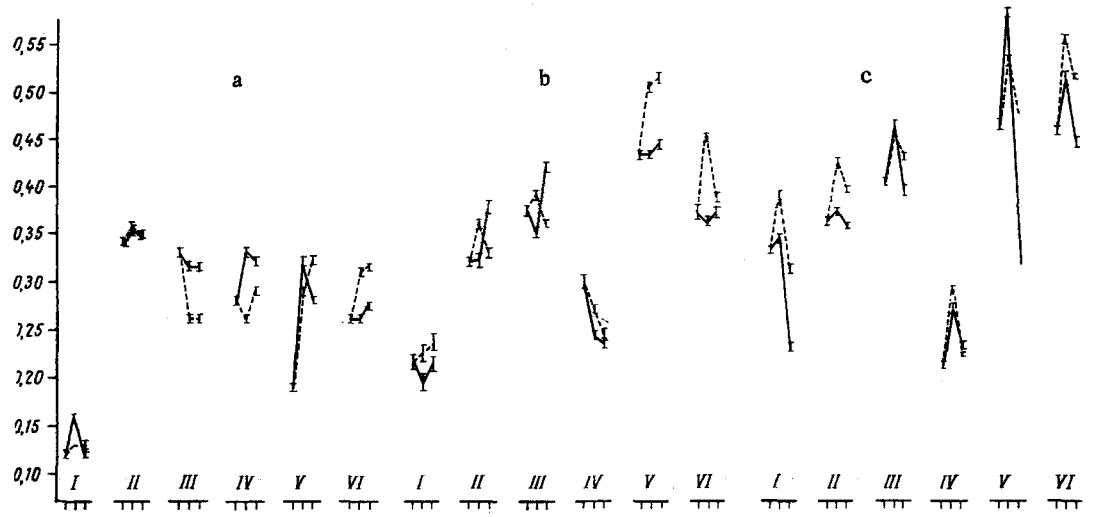

Fig. 1. Dynamics of enzyme activity in animals receiving preliminary treatment with gutimin (b) and izatin (c) and in control group receiving GHBA (a). Abscissa, stages of biopsy of myocardium; ordinate, increase in optical density during 1 min. I) LD; II) SD; III) SD/PMS; IV) NADPH-diaphorase; V) α-GPC; VI) α-GPM. PMS) phenazine metasulfate.

hematoxylin and eosin. Enzyme activity was estimated quantitatively with the MUF-5 scanning microspectrophotometer at 546 nm with a 1-μ probe [1, 2]. Activity of the enzymes was expressed as the increase in optical density per minute. The results were subjected to statistical analysis on the ÉVM-40-30 computer, using a special program.

EXPERIMENTAL RESULTS

In all groups of animals throughout the period of the experiment the blood pressure and heart rate did not change significantly. In the animals of group 1, however, 20-30 min after RCBF a disturbance of the rhythm was observed (marked ventricular extrasystoles, sinus rhythm), which persisted for 15-30 min. In the animals of the second and control groups, the above-mentioned disturbances were not observed. Signs of ischemia were noted in epicardial ECG leads 1 min after ligation of CA. The tensometric results showed that the work of the left ventricle was substantially unchanged outside the zone of ischemia throughout the experiments. In the zone of ischemia work of the myocardium was reduced in the control group with effect from the first 5-8 min and it ceased 20 min after ligation of CA; in the gutimin group it was 70-75% of the initial level at the moment of RCBF, falling to 50-60% 90 min after RCBF. In the animals of group 2 no tensometric investigations were undertaken.

In all groups investigated before mobilization of CA, a high glycogen concentration and high phosphorylase activity were found in the myocardium of the left ventricle. In all animals ischemia for 90 min led to a marked fall in the glycogen level and phosphorylase activity. The glycogen level and phosphorylase activity fell most of all in the animals of group 2, rather less so in the dogs of group 1, and less still in the animals of the control group. In the intact zone, no changes were observed in the glycogen level or phosphorylase activity in any of the groups. Restoration of the coronary blood flow also led to partial recovery of the glycogen level and to an increase in phosphorylase activity in the zone of ischemia; the changes were most marked in animals receiving izatin, less so in those receiving gutimin. In the animals of the control group these changes were slight in degree and focal in character.

As Fig. 1b shows, ischemia for 90 min led to marked activation of enzymes in the zone of ischemia, whereas in the intact zone these changes were absent. In the animals of group 2 and the control group (Fig. 1c, a), on the other hand, the dynamics of enzyme activity was similar in direction in both zones although the changes were more marked in the zone of ischemia. By contrast with the animals of group 1 and the control group, in group 2 marked activation of LD was observed in the zone of ischemia. The pyruvate formed during glycolysis was evidently converted into lactate with elimination of glycolytic NADH [8, 10]. In this

respect izatin differs advantageously from GHBA and gutimin which, as the results given above show, had no marked effect on LD activity. It must be emphasized that under conditions of ischemia the lactate pyruvate system in the myocardium cannot be a sufficiently effective means of pyruvate utilization, for one of the LD isozymes in the myocardium is inhibited by low concentration of pyruvate. Nevertheless, there is another pathway of NADH utilization in the myocardium, which incorporates utilization of the excess of pyruvate in the presence of succinate and CO_2, which is converted in the myocardium (mitochondria) into oxaloacetic acid [9, 13]. However, this pathway requires the presence of a reduced equivalent of NADH, which is supplied to the mitochondrion under conditions of ischemia by α-glycerophosphate, malate-aspartate, and oxaloacetate shunts.

If the changes observed in the myocardium of the animals in these experiments are examined from these standpoints it can be concluded that only izatin enables the above-mentioned pathways of utilization of glycolytic NADH and pyruvate to be most fully and effectively utilized in the myocardium. As Fig. 1c shows, under the influence of izatin simultaneous activation of the LD system, the α-glycerophosphate shunt, and the SD system took place in the stage of acute ischemia.

The results obtained by the study of the dynamics of NADPH-diaphorase are interesting. We know [6, 13] that NADPH-dependent enzymes and, in particular, enzymes of the pentose phosphate pathway participate in the regulation of activity of the conducting system of the myocardium, and so largely determine the degree of disturbance of the function of this system. The results of the present experiment showed that gutimin inhibits NADPH-diaphorase activity in both zones of the myocardium at all stages of the experiment. Conversely GHBA and, in particular, izatin stimulate the activity of this enzyme in both zones of the myocardium.

LITERATURE CITED

1. G. G. Avtandilov and E. N. Nesterov, Byull. Éksp. Biol. Med., No. 4, 82 (1971).
2. G. G. Avtandilov, Morphometry in Pathology [in Russian], Moscow (1973).
3. V. M. Koryukin, V. A. Grantyn', and V. A. Pryanishnikov, Vestn. Khir., No. 3, 152 (1977).
4. R. I. Megrelishvili, R. I. Glazer, V. N. Artamonov, et al., Kardiologiya, No. 7, 57 (1975).
5. Z. G. Ovrutskaya, A. A. Tsyganii, G. Yu. Nem, et al., in: Abstracts of Proceedings of the Second Congress of Anesthesiologists and Reanimatologists of the Ukrainian SSR [in Russian], Kiev (1974), pp. 82-84.
6. V. G. Popov, D. A. Kharkevich, A. L. Syrkin, et al., Ter. Arkh., No. 12, 44 (1968).
7. E. P. Stepanyan and I. N. Barkan, The Energy Metabolism of the Heart during Operations [in Russian], Moscow (1971).
8. G. V. Chernyshova, M. D. Vagar, E. V. Bogdanova, et al., Byull. Éksp. Biol. Med., No. 11, 572 (1977).
9. B. M. Shargorodskii and O. L. Morozova, Kardiologiya, No. 11, 107 (1974).
10. N. Brachfeld, Kardiologiya, No. 12, 117 (1972).
11. A. J. Brink, A. J. Bester, and A. Lochner, J. Mol. Cell. Cardiol., 2, 71 (1971).
12. C. Guimbi et al., Anesth. Analg. Curr. Res., 53, 334 (1974).
13. H. Laborit, The Regulation of Metabolic Processes [Russian translation], Moscow (1970).