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# CORRECTION OF EXPERIMENTAL ATHEROSCLEROSIS BY Co-35

**Kh. N. Dzhuraev and N. N. Nasriddinova**

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**KEY WORDS:** atherosclerosis; nitro preparations; beta-blockers; cobalt; lipid metabolism

Modern agents for the treatment of atherosclerosis and ischemic heart disease, including nitro preparations, beta-blockers, and calcium antagonists, are insufficiently effective in the prevention of myocardial infarction or in reducing patient motality. According to some reports [11], beta-blockers may have an atherogenic action on the body. For this reason the search for new therapeutic agents both for IHD and for atherosclerosis still remains an urgent problem in medicine. We know that cobalt preparations have a hypolipidemic action in atherosclerosis [1-6, 9, 10]. Positive changes in enzyme-dependent processes and reactivity of the cardiovascular system under the influences of small doses of cobalt and its preparations have been described [7, 10].

The aim of this investigation was to study the efficacy of Co-35, a complex compound of cobaltous chloride with an organic substance, and its effect on lipid metabolism and on the blood clotting system.

## EXPERIMENTAL METHOD

Rabbits (21) weighing 2.6-2.9 kg were fed for 6 months on cholesterol and developed experimental atherosclerosis. Rabbits (6) of the control group received physiological saline. The group of rabbits for study was divided into two groups: group 1 (7) received 1 mg/kg of Co-35, Group 2 (7) received cobaltous chloride in the same dose for one month. Blood levels of cholesterol, lecithin, beta-lipoproteins, phospholipids, and free fatty acids were determined in all the rabbits before, during, and after treatment. Free fatty acids were investigated on the LKhM-8 MD-5 chromatograph, and in a parallel series, on the Khrom-1 instrument. Phospholipid fractions were determined by thin-layer chromatography. Parameters of the blood clotting system were determined simultaneously by the coagulogram method. The results were subjected to statistical analysis by Oivin's method [8]. During analysis of the

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results possible correlations between lipid metabolism and blood clotting parameters were taken into consideration. In the course of the investigation one rabbit of group 2 developed thrombosis of the cerebral vessels with right-sided hemiplegia. Blood was taken from the marginal vein of the rabbit's ear before the experiment and 15 and 30 days after the beginning of the course of treatment with Co-35.

## EXPERIMENTAL RESULTS

In rabbits with experimental atherosclerosis before treatment with Co-35 a marked increase was observed in concentrations of cholesterol (15.17 ± 1.93 mmoles/liter; $p < 0.001$), beta-lipoproteins (6.88 ± 0.44 mmoles/liter; $p < 0.001$), and lecithin (2.52 ± 0.18 mmoles/liter; $p < 0.001$) with a significant difference compared with data for healthy rabbits. Deviations also were observed in the phospholipid fraction: an increase in lysolecithin (24.07 ± 75 mg%; $p < 0.001$), sphingomyelin (17.74 ± 0.42 mg%; $p < 0.001$), lecithin (52.46 ± 2.38 mg%; $p < 0.001$), and kephalin (18.78 ± 1.11 mg%; $p < 0.001$); a decrease in phosphatidylserine (7.93 ± 0.23 mg%; $p < 0.1$), polyglycerophosphatidic acid (4.86 ± 0.18 mg%; $p < 0.1$). Total phospholipids were increased (134.10 ± 3.23 mg%; $p < 0.001$). Determination of free fatty acids revealed an increase in saturated and a decrease in unsaturated forms.

The study of blood clotting parameters revealed hypercoagulation: shortening of the blood clotting time by 19.67%, heparin time by 6.25%, and plasma recalcification time by 42.04%, an increase in the fibrinogen concentration by 26.7%, in the prothrombin index by 13.49%, and the thrombin test by 16.3% compared with normal. Besides a change in the blood clotting system, inhibition of the anticlotting system of the blood was observed: reduction of fibrinolytic activity of the blood by 48.86%, of the free heparin level of the blood by 45.43%, and of blood antithrombin activity by 15.98%.

An increase in plasma heparin tolerance by 36.54% and in the thrombin time by 15.94% was discovered mainly in rabbits with marked hyperlipidemia, and was attributed to an adaptive phenomenon, protecting against thrombosis.

A comparative study of lipids and of parameters of the blood clotting system revealed the existence of correlation, which was particularly strong in the case of comparison with cholesterol and beta-lipoproteins, on the one hand, and the clotting time and prothrombin index of the fibrinolytic system of the blood, on the other hand.

On visual observation the rabbits receiving cholesterol looked older than their age, they were lethargic and adynamic and their fur and eyes were dull; their weight increased on average by 225 g.

When Co-35 treatment was given concentrations of cholesterol (10.07 ± 1.16 mmoles/liter; $p < 0.05$) and beta-lipoproteins (5.35 ± 0.28 mmoles/liter; $p < 0.01$) and an increase in lecithin (3.21 ± 0.21 mmoles/liter; $p < 0.05$) were observed.

The study of the phospholipid fraction revealed an increase after administration of Co-35 in concentrations of phosphatidylserine (9.33 ± 0.49 mg%; $p < 0.02$), phosphatidylinositol (9.73 ± 0.8 mg%; $p < 0.05$), and polyglycerophosphatidic acid (5.72 ± 0.23 mg%; $p < 0.02$), whereas the remaining fractions – lysolecithin (16.47 ± 0.77 mg%; $p < 0.001$), sphingomyel in (112.27 ± 0.55 mg%; $p < 0.001$), lecithin (45.15 ± 2.18 mg%; $p < 0.05$), and kephalin (13.81 ± 0.54 mg%; $p < 0.001$), and total phospholipids (112.48 ± 2.92 mg%; $p < 0.001$) were reduced, although not to the normal level (5.72 ± 0.23 mg%; $p < 0.02$).

So far as parameters of the blood clotting system are concerned, in most rabbits with experimental atherosclerosis favorable changes were observed after treatment with Co-35 toward hypocoagulation: slowing of the blood clotting time (by 89.09%), reduction of the plasma heparin tolerance (by 54.19%), slowing of the plasma recalcification time (by 70.98%), lowering of the fibrinogen concentration (by 10.72%) and the prothrombin index (by 20.25%), a fall in the level of the thrombin test (by 47.72%) and of the antithrombin activity of the blood (by 14.57%). In addition, the increase in the free heparin concentration in the blood (by 16.92%) and in fibrinolytic activity of the blood (by 68.99%) pointed to hypocoagulation.

In a comparative study of Co-35 and the inorganic cobalt salt cobaltous chloride, the latter had no significant effect on lipid metabolism or on the blood clotting system.

It can be concluded from this investigation that Co-35 has a beneficial effect on disturbed lipid metabolism and on the manifestations of hypercoagulation in experimental atherosclerosis.

The results are such that Co-35 can be recommended as an effective agent for the prevention and treatment of atherosclerosis.

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