INFLUENCE OF VANADYL SULFATE ON HYPERCHOLESTERINEMIA FOLLOWING A SINGLE INJECTION OF CHOLESTEROL

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We had earlier demonstrated that after a single injection of a large dose of cholesterol into rabbits, there is a prolonged increase in its content in the blood serum. It was hypothesized that this hypercholesterinemia may be used to study the hypotholesterinemic action of drugs [1].

In this work we investigated the influence of vanadyl sulfate on the cholesterol content in the blood serum, using the model indicated above.

The undertaking of experiments of this kind was based upon the fact that the antiatherogenic influence of this preparation has been described by a number of authors [2, 7, etc.], while its hypocholesterinemic properties have been insufficiently convincingly demonstrated. And yet, these properties may play a vital role in the mechanism of the action of vanadyl sulfate during experimental atherosclerosis.

EXPERIMENTAL PROCEDURE

The experiments were conducted on male rabbits weighing 2.5-3 kg. Cholesterol was injected in the form of a 5% solution in sunflower oil through a probe into the stomach in a dose of 1 g per kg of weight. Four series of experiments were conducted: the rabbits of series I (13 animals) received cholesterol and subcutaneous injections of physiological saline; the animals of series II (10) received vanadyl sulfate ($VOSO_4 \cdot 2H_2O$) in a dose of 1 mg/kg subcutaneously 23 h after the administration of cholesterol; the rabbits of series III (10) received daily subcutaneous injections of vanadyl sulfate, 1 mg/kg per day, for a period of five days (the first injection was performed 23 h after the administration of cholesterol); the animals of series IV (10) received twice daily injections of vanadyl sulfate in a dose of 2.5 mg/kg (daily dose 5 mg/kg) for five days (first injection 23 h after the beginning of the experiment).

In all the animals we determined the cholesterol content in the blood serum after 23, 24, 25, 27, 29, 48, 72, 96, 120, 168 and 240 h following its introduction into the stomach. A micromethod of determining cholesterol was used (0.2 ml of serum, which was extracted with Blure's alcohol-ether mixture according to the method described in S. D. Balachovskii's Handbook, was taken for the analysis).

RESULTS OF THE INVESTIGATIONS

A single introduction of cholesterol into the stomach led to a distinct increase in its content in the blood serum (Fig. 1). After 23 h the cholesterol level had almost doubled. By the twenty-ninth hour, a further, but indistinct increase in its content was noted. After 48 h, the cholesterol level was almost five times as great as the normal indices, while 72 h after cholesterol loading, the maximum rise in the hypercholesterinemic curve was noted. From this time on, there was a decrease in the cholesterol content in the serum, which continued for several days. Only after 240 h did the cholesterol level practically return to normal (Fig. 2).

*Deceased.

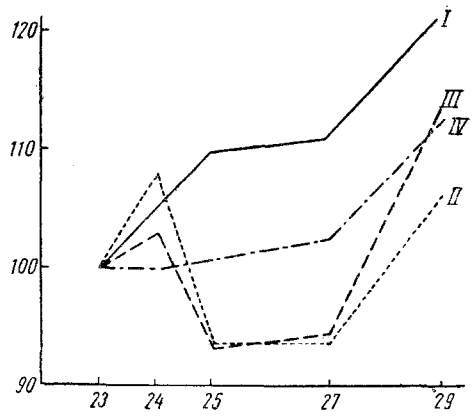

Fig. 1. Variation of the blood serum cholesterol content during the first hours after the injection of vanadyl sulfate. Along X-axis—time in hours; along Y-axis—cholesterol content in % (the amount of serum cholesterol 23 h after injection of cholesterol, i.e., directly after injection of the preparation, was taken as 100). I) Administration of cholesterol only (control); II) administration of cholesterol and vanadyl sulfate (1 mg/kg, once); III) administration of cholesterol and vanadyl sulfate (1 mg/kg for five days); IV) administration of cholesterol and vanadyl sulfate (5 mg/kg for five days).

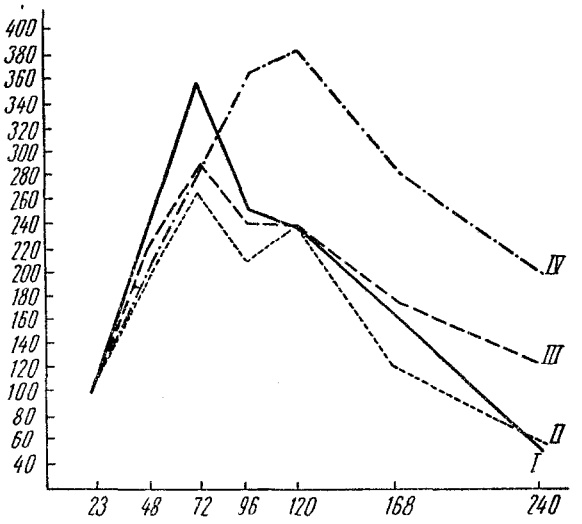

Fig. 2. Variation of the serum cholesterol content during long-term periods after the injection of vanadyl sulfate. Notations the same as in Fig. 1.

As can be seen from Fig. 1, two hours after the injection of vanadyl sulfate in a dose of 1 mg/kg, the cholesterol level was lower than in the control (by the twenty-fifth hour). By the twenty-ninth hour (by the sixth hour after injection of the preparation), the cholesterol content had begun to rise gradually. However, during the following periods of observation, the cholesterol level in the experimental series was lower than the control, just as before. The maximum difference in the intensity of hypercholesterinemia was noted 72 h after the administration of cholesterol (see Fig. 2). During this period the cholesterol content in the control was 271 ±27.7 mg%, and in the experimental group 169 ±20.9 mg% (P = 0.01). After five days (120 h), the differences in the experimental and control groups decreased. The establishment of a normal level was noted at the same periods in both series.

In the experimental series III (preparation was administered repeatedly in a dose of 1 mg/kg per day for five days), during the first hours after the injection, a negligible lag in the increase in the cholesterol level was noted in comparison with the control, just as in the experimental series II. Subsequently the intensity of hypercholesterinemia in the experimental group changed just as in the control. However, at the end of the observation period, the rate of decrease in the serum cholesterol slowed down in the animals that received vanadyl sulfate. The cholesterol level in the experimental series was twice as great as that in the control 24 h after the administration of cholesterol.

In the last series of experiments, vanadyl sulfate was administered in a dose of 2.5 mg/kg, twice a day. It is interesting that when this dose was administered, during the first hours the hypocholesterinemic action of the preparation practically was not manifested, while beginning with the fourth day (96 h), the cholesterol content subtially exceeded the level in the control, reaching a maximum after 120 h (in the control, after 72 h). The decrease in the cholesterol content in the blood serum in this series was extremely slow. A higher cholesterol level in the experimental group in comparison with the control was retained all the way up to the end of the experiments (see Fig. 2). The cholesterol content in the blood serum was normalized 14 days after cholesterol loading.

Generalizing the results of our investigations, let us emphasize that vanadyl sulfate may exert varied influences upon the increased cholesterol content in the blood serum, depending upon the dose and system of its application. In the case of repeated administration of this preparation in a dose of 1 mg/kg, hypercholesterinemia in the experimental series was somewhat less pronounced than in the control (a reliable difference was noted only 72 h following the administration of cholesterol). In the case of repeated administrations of the same dose over a period of several days, during the first hours of the investigation we observed a certain inhibition of the increase in the serum cholesterol

in comparison with the control. At the very end of the experiment, the cholesterol level in the blood serum of the animals that received the preparation was higher than among control rabbits. The slowdown of the normalization of the cholesterol level was even more pronounced in the case of the use of a larger dose of vanadyl sulfate (5 mg/kg), after the administration of which a sharp intensification of hypercholesterinemia was noted.

From the literature it is known that vanadium ions inhibit cholesterol biosynthesis in the liver [4, 5, 7, 11, 14 etc.]. However, the decrease in the cholesterol content in the blood serum observed in our experiments is difficult to explain by the influence of vanadium precisely upon this process, since it has been established that the taking of cholesterol with food sharply inhibits its synthesis in the liver [3, 8-10, 13, etc]. Some authors [12] believe that vanadium may influence the processes both of formation and of decomposition of cholesterol in the organism, stimulating the latter. Although this has not been demonstrated experimentally, the idea of an intensification of the reactions of cholesterol catabolism is extremely attractive as an explanation of the hypocholesterinemic action of vanadium. In addition, it may be hypothesized that under certain conditions vanadium may inhibit enzymatic processes participating in the decomposition of cholesterol. To this is evidently due the deceleration of the normalization of the cholesterol level, noted in experiments with the use of vanadyl sulfate in dose of 1 and 5 mg/kg for five days. It is interesting that we detected such an action after administration of this preparation in a dose of 10 mg/kg to irradiated animals, in which distinct hypercholesterinemia had developed. A single administration of a large dose of vanadyl sulfate sharply intensified "radiation" hypercholesterinemia.

Thus, as a result of our experiments it was established that depending on the dose and system of administration, vanadyl sulfate may either weaken or intensify dietary hypercholesterinemia. When this preparation is used for therapeutic purposes, in our opinion, the different nature of its influence upon the serum cholesterol should be taken into consideration, since the intensification of hypercholesterinemia aggravates the course of atherosclerosis.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.