EFFECT OF COMBINED ADMINISTRATION OF para-AMINOBENZOIC ACID (PABA) AND β-SITOSTEROL ON THE COURSE OF EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS

(UDC 616.13-004.6-085.415.7-07:616-003.826-092.9)

A. F. Ryzhova

Department of Pharmacology (Head—Prof. T. A. Mel'nikova)
Institute of Chemopharmaceutics, Leningrad
(Presented by Member of the Academy of Medical Sciences, USSR, S. V. Anichkov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 60, No. 8, pp. 83-85, August, 1965
Original article submitted March 17, 1964

The plant sterols, especially β-sitosterol, are given great prominence in the treatment of atherosclerosis. As early as 1929, it was shown [9] that β-sitosterol, in contrast to cholesterol, is not absorbed from the intestine. A number of authors [5, 6, 7, 8, 9] noted later that β-sitosterol inhibits the absorption of exogenous cholesterol. According to some findings [1], β-sitosterol promotes increased evolution of bile acids and oxidation of cholesterol in the liver.

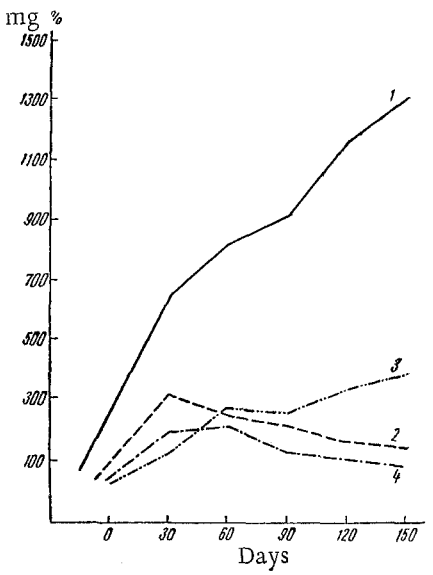
On the other hand, we have shown [2] that PABA intensifies the breakdown of endogenous cholesterol and promotes more rapid resorption of lipid infiltrates during the involution of atherosclerosis.

In the present work we have studied the effect of joint administration of 2 preparations, PABA and β-sitosterol, which block different links of cholesterol accumulation, during experimental atherosclerosis.

EXPERIMENTAL METHODS

The studies were of 23 male rabbits weighing 2.5-3 kg. Atherosclerosis was induced by the method of N. A. Yushchenko [4].

The severity of the atherosclerosis was evaluated from the level of cholesterol and phospholipids in the blood serum, the cholesterol content of liver and aorta, and the amount of lipids extracted chemically from the aorta walls after the rabbits were killed.



Contents of cholesterol and lecithin in the blood serum of rabbits. 1, 3) Control groups; 2, 4) experimental groups.

EXPERIMENTAL RESULTS

There were two groups of rabbits. The first group (10 rabbits) was the control. These animals were given daily for 20 weeks 0.3 g cholesterol per kg in 30 g minced vegetables and physiological saline subcutaneously. A rapid increase in blood serum cholesterol, up to 1332±111 mg % by the end of the trial (see figure), and a relatively low lecithin content (in relation to that of cholesterol), up to 417±55 mg %, were observed in the animals of that group. The cholesterol-lecithin index in that group of rabbits was 3.2.

After observation for 20 weeks the animals were killed. The whole length of the aorta up to its bifurcation was extracted. In most control rabbits thickening of the aorta walls due to the formation of large confluent atheromatous plaques yellowish to whitish in color were visible macroscopically. The plaques appeared in considerable numbers in the

TABLE 1. Average Amounts of Lipids in the Aorta (in mg)

Group	Weight of aorta	In whole aorta	In 100 mg aorta tissue
Control	982±67,3	118±11,9	12±0,7
Experimental	762±27,8	46,3±13	5,8±0,42

TABLE 2. Average Cholesterol Content of Liver and Aorta (in mg)

Group	In liver	In aorta	
		total	in 100 mg
Control	879,3±73,3	12±1,9	1,5±0,03
Experimental	417,6±63	5,2±1,3	0,6±0,1

lumen of the aorta, especially in its thoracic section. The amount of lipids per 100 mg aorta tissue was 12.7±0.7 mg (Table 1).

The amount of cholesterol in liver was quite high, 879±73 mg %, and the cholesterol content of the wall of the whole aorta was on average 12±1.9 mg (Table 2).

The animals of the 2nd experimental group (13 rabbits) were given 0.3 g/kg cholesterol and 0.5 g/kg β-sitosterol by mouth and 5 mg/kg PABA in a 5% solution subcutaneously. The last 2 preparations were administered to the animals 30 min before the cholesterol; β-sitosterol purified by the method of A. M. Khaletskii [3] and containing 95.6% pure preparation was used.

As the figure shows, the level of cholesterol and lecithin in the serum of the experimental animals increased extremely slowly. By the 12th week of observation the cholesterol level had reached 250±34.5 mg % and that of lecithin 156±12 mg %. By the end of the trial (in the 20th week) the lecithin content had returned to normal (98.8 mg %), and the cholesterol level remained somewhat elevated (156 mg %) compared with the normal. The cholesterol-lecithin index in the experimental group was 1.4(normal=1).

The results of pathological and morphological studies of the vessels are of special interest. In most animals the aorta was elastic, with lustrous intima most of the way along, and there was a slight accumulation of atheromatous plaques in the thoracic section of the aorta scattered about in the form of isolated islets of spots.

In 4 rabbits the accumulation of atheromatous formations in the aorta was somewhat more pronounced; the plaques had the appearance of thickened whitish strands or fused islets. The average amount of lipids (see Table 1) per 100 mg aorta tissue was 5.8±0.42 mg.

The level of cholesterol in the liver was half and in the aorta wall two fifths of that in the control group of rabbits (see Table 2).

When only β-sitosterol was administered to the rabbits, from the 12th week of observation (same experimental conditions) "breakthrough" of exogenous cholesterol into the blood is seen with subsequent deposition in the liver and vascular walls, whereas the combination of PABA and β-sitosterol prevented the "breakthrough" of cholesterol into the blood during a long-term (20-week) trial with a constant cholesterol loading.

The prevention of any disturbance in the cholesterol-lecithin balance at later periods (over 3 months of the trial) should apparently be explained by increased breakdown of cholesterol in the liver under the influence of PABA, as the amounts of β-sitosterol used by us (1:1.7) were considerably smaller than those mentioned in the literature.

According to some findings [8], complete blocking of cholesterol absorption from the intestine is possible only with a cholesterol to β-sitosterol ratio of 1:6 - 1:7.

The results of our trials show that the combined use of the two preparations PABA and β-sitosterol, which are capable of blocking cholesterol accumulation at different levels and of practically preventing the disturbance of the cholesterol-lecithin balance in the experimental animals, is advisable.

SUMMARY

This research is devoted to the study of the combined effect of 2 preparations (PABA and β-sitostyrene) with different mechanisms of the antisclerotic effect. In a comparative estimation of the basic indices in control and test animals (cholesterol and phospholipid content of the blood serum, cholesterol level in the liver and aorta, as well as number of lipids in the aortic wall) it was found that injection of the above combination of preparations prevented disturbance of the cholesterol-lecithin balance in test animals to a considerable extent in spite of a prolonged cholesterol administration (20 weeks).

LITERATURE CITED

1. K. A. Meshcherskaya, G. P. Borodina, and N. P. Koroleva et al., Farmakol. i toksikol., 5 (1959), p. 434.
2. A. F. Ryzhova, Byull. éksper. biol., 7 (1963), p. 52.
3. A. M. Khaletskii, Med. prom. SSSR, 11 (1961), p. 32.
4. N. A. Yushchenko, Byull. éksper. biol., 3 (1959), p. 31.
5. W. W. Davis, Trans. New York Acad. Sci., 18 (1955), p. 123.
6. M. Fraser and F. Gardner, Proc. roy. Soc. B., 82 (1910), p. 559.
7. H. H. Hernander and I. L. Chaikoff, Proc. Soc. exp. Biol. (New York) 87 (1954), p. 541.
8. D. W. Peterson, Proc. Soc. exp. Biol. (New York) 78 (1951), p. 143.
9. R. Schoenheimer and Heylers-Hoppe, Z. physiol. Chem., 180 (1929), p. 1.

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.
