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EFFECT OF ETHYRAZOLE AND PARMIDINE ON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS

V. E. Ryzhenkov, É. M. Tararak,
G. G. Khechinashvili, and I. V. Mosina

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In rabbits receiving cholesterol with the diet for 3-4 months the accumulation of total cholesterol in the aorta and the degree of severity of atherosclerosis of the aorta were reduced by administration of ethyrazole and parmidine. These substances had no substantial effect on the blood cholesterol, triglyceride, and phospholipid levels of these animals.

KEY WORDS: aorta; lipids; atherosclerosis.

Previous investigations have shown that the compound ethyrazole (bis-methylamide-1-ethylpyrazole-3,4-dicarboxylic acid) has a marked antiinflammatory action [4]. A similar property is found in the structurally closely related compound pyridinol carbamate (bis-N-methylcarbamino ester of 2,6-bis-hydroxymethylpyridine) [7, 11], which has been used with success for the prevention and treatment of atherosclerosis and ischemic heart disease [8, 12].

Considering the role of changes in the blood vessel wall in the pathogenesis of atherosclerosis [9, 12] and also data showing the ability of pyridinol carbamate to prevent the penetration of atherogenic lipoproteins into the arterial wall [12], an investigation was carried out to compare the effect of ethyrazole and parmidine, a Soviet preparation of pyridinol carbamate synthesized at the All-Union Pharmaceutical Chemical Research Institute, on lipid metabolism and experimental atherosclerosis in rabbits.

EXPERIMENTAL METHOD

In experiments with ethyrazole, male rabbits (2.3-2.7 kg) were given cholesterol (0.3 g/kg) and the compound (30 mg/kg) with the diet for 3 months, and in the experiments with parmidine the rabbits received cholesterol (0.25 mg/kg) and the compounds (10 mg/kg) for 4 months. Animals of the control groups received cholesterol alone in the above amounts. The blood serum levels of total cholesterol [6], triglycerides [10], phospholipids [13], and total lipids [14] were determined. The animals were killed by injection of air into the auricular vein, the aorta was removed along its whole length, measured by planimetry [1], and its total cholesterol content was determined. The content of cholesterol and total lipids in the liver was determined. In the rabbits receiving cholesterol alone or cholesterol with parmidine the aorta also was investigated morphologically, with quantitative estimation of lipids in individual plaques in different parts of the aorta, using the stereological principle [3, 5]. The numerical results were subjected to statistical analysis [2].

Laboratory of Experimental Pharmacotherapy, N. N. Anichkov Department of Atherosclerosis, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 81, No. 5, pp. 558-559, May, 1976. Original article submitted October 8, 1975.

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TABLE 1. Effect of Ethyrazole and Parmidine on Lipid Content in Aorta and Liver of Rabbits with Experimental Atherosclerosis ($M \pm m$)

Compound	Group of animals	Aorta	Liver	
		cholesterol (in mg/g wet weight of tissue)	cholesterol (in mg/g wet weight of tissue)	total lipids (in mg/g wet weight of tissue)
Ethyrazole	Intact	3,0 ± 0,6 (5)	4,5 ± 0,9 (5)	22,1 ± 3,5 (5)
	Receiv. cholesterol (0,3 g/kg) for 3 months	33,9 ± 6,0 (6)	80,5 ± 4,8 (6)	110,9 ± 8,4 (6)
	Receiving cholesterol (0,3 g/kg) + ethyrazole (30 mg/kg) for 3 months	16,3 ± 3,3 (7)†	64,7 ± 4,4 (7)†	88,8 ± 6,7 (7)†
Parmidine	Intact	3,4 ± 0,5 (6)	4,2 ± 0,67 (6)	39,5 ± 4,3 (6)
	Receiving cholesterol (0,25 g/kg) for 4 months	38,8 ± 6,0 (6)	58,3 ± 6,3 (9)	167,5 ± 22,3 (9)
	Receiving cholesterol (0,25 g/kg) + parmidine (10 mg/kg) for 4 months	16,7 ± 1,8 (6)†	32,0 ± 4,5 (9) *	83,7 ± 11,2 (9)†

Legend. Number of animals in parentheses.

* $P < 0.01$,

† $P < 0.05$.

EXPERIMENTAL RESULTS AND DISCUSSION

Ethyrazole and parmidine had a marked antiatherosclerotic action. After their administration the index of severity of atherosclerosis in the aortas of the rabbits was reduced by more than half compared with that of animals receiving cholesterol alone. In the experiments with ethyrazole this index was $19.7 \pm 7.1\%$ compared with $52.3 \pm 9\%$, and in the experiments with parmidine it was $19.2 \pm 4.6\%$ compared with $40 \pm 5.2\%$. Under the influence of these substances the total cholesterol content in the aorta and liver of the rabbits fell (Table 1). Comparative determination of the relative content of lipids in plaques in the arch of the aorta and in the thoracic and abdominal portions of the aorta in animals receiving and not receiving parmidine together with cholesterol revealed a significant decrease in their content under the influence of the compound in the arch of the aorta ($0.3 \pm 0.018\%$ compared with $0.37 \pm 0.024\%$; $P < 0.05$) and a tendency for it to decrease in the abdominal part ($0.22 \pm 0.034\%$ compared with $0.31 \pm 0.032\%$). This may indicate that parmidine can remove lipids from formed atherosclerotic plaques in animals.

Meanwhile no significant differences were observed in the content of cholesterol, triglycerides, phospholipids, and total lipids in the blood serum of the rabbits receiving and not receiving ethyrazole or parmidine along with cholesterol.

The antiatherosclerotic action of the two compounds was thus exhibited without any effect on the blood lipid level. According to Shimamoto [12], pyridinol carbamate possesses similar properties, and prevents the penetration of atherogenic lipoproteins into the blood vessel wall. The structural similarity between the molecules of pyridinol carbamate (parmidine) and ethyrazole (the aromatic character of the rings, the presence of methylamide groups) may explain the presence of the same properties in the latter compound also. The mechanism of the antiatherosclerotic action of ethyrazole and parmidine is probably connected with their ability to exert an antiinflammatory action.

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