The Use of Alisat to Control Lipids and Lipid Peroxidation Products in the Blood of Patients with Atherosclerosis

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The use of Alisat for the treatment of patients with ischemic heart disease prevents the development of undesirable proatherogenic effects of prolonged therapy with the nonselective β-adrenoblocker, obsidan. Combined treatment with Alisat and obsidan was not accompanied by a decrease in plasma levels of high-density lipoprotein cholesterol and apolipoprotein A-I, an increase in the contents of conjugated dienes and malonic dialdehyde, and a decrease in the activity of glutathione peroxidase. However, prolonged obsidan monotherapy led to these changes.

Key Words: *garlic; β-adrenoceptor-blocking agents; atherosclerosis; cholesterol; lipid peroxides; lipoproteins*

High plasma concentrations of cholesterol (CS) and triglycerides, α-hypocholesterolemia (low level of CS in high-density lipoproteins, HDL), and activation of lipid peroxidation (LPO) accompanied by accumulation of LPO products and peroxidative modification of blood plasma lipoproteins contribute to the development and pathogenesis of atherosclerosis [1,2,14]. The primary goal of hypolipidemic and antioxidant therapy preventing the development of atherosclerosis is to control these processes. Besides the well-known pathogenic mechanisms of lipid metabolic disturbances in patients with atherosclerosis, there are iatrogenic atherogenic changes in lipid metabolism associated with adverse effects of prolonged therapy with antianginal drugs. For example, prolonged therapy with the nonselective β-adrenoceptor-blocking agent, obsidan (an antianginal drug), decreases plasma concentrations of HDL CS and apolipoprotein A-I and increases the contents of triglycerides and apolipoprotein B [12]. Our studies showed that a 2-3-month treatment with obsidan leads to the increase in plasma levels of primary and secondary LPO products, conjugated dienes (CD), and malonic dialdehyde (MDA). This indicates the activation of LPO processes [2]. These changes in plasma lipids require an apropos correction. However, traditional hypolipidemic drugs are not necessarily appropriate due to their adverse effects. In this aspect, the use of natural plant-derived medicines (for example, Alisat obtained from garlic) is of practical interest. Alisat displays moderate hypolipidemic and antioxidant activity [3,4], decreases the proliferative activity of fibroblasts and the accumulation of CS in smooth-muscle cells [6,10], and does not have adverse effects [5].

Here we studied the possible use of Alisat for the treatment of patients with atherosclerosis to prevent adverse atherogenic changes in LPO and blood lipids induced by prolonged therapy with obsidan, a nonselective β-adrenoceptor-blocking agent.

MATERIALS AND METHODS

Blood samples of 68 patients with atherosclerosis (ischemic heart disease and type II stable effort angina pectoris) treated with obsidan (as an anti-

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anginal drug, 160-240 mg/day) for 6 months were studied. Obsidan and Alisat (2 tablets/day) were simultaneously given to 23 of these patients (the main group); 45 patients received obsidan monotherapy (control group). Blood was taken from the cubital vein in the morning (no less than 12 h after food uptake) before the beginning and after 0.5, 1, 2, 3, 4, and 6 months of therapy. The plasma content of DC was estimated by measuring their optical density at 233 nm. The concentration of MDA was determined by the reaction with 2-thiobarbituric acid at 532 nm. The results of these measurements were expressed as D_{233} and D_{532}, respectively (per 1 ml plasma). The activity of the key antioxidant enzyme, erythrocytic glutathione peroxidase, was assayed by analyzing NADH oxidation in a coupled glutathione reductase system. t-Butyl peroxide was used as the substrate. Plasma concentrations of CS and triglycerides were measured using Boehringer enzyme kits. The content of HDL CS was estimated by precipitation of low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) with the manganese-heparin reagent. Total plasma lipids were determined using a Lachema kit. The content of LDL CS was calculated from the following formula: CS-HDL — CS-tryglycerides/5. Plasma levels of apolipoproteins A-I and B were measured in MSS-340 multiscanner (Labsystems) and SF-26 and Beckman DU-65 spectrophotometers by a solid-phase enzyme immunoassay in polystyrene plates with monospecific rabbit antibodies. The results were statistically analyzed by the Student difference method.

RESULTS

Studies of the initial intensity of LPO processes in the blood showed that the contents of CD and MDA were significantly higher and the activity of erythrocytic glutathione peroxidase was lower in patients with ischemic heart disease of the main and control groups compared with these parameters in healthy individuals. We revealed high concentrations of CS, LDL CS, and apolipoprotein B and low concentrations of HDL CS and apolipoprotein A-I typical of patients with atherosclerosis (Table 1). In control patients, the content of HDL CS decreased on the second month of obsidan therapy. Its concentration decreased by 18% on the sixth month of therapy. On the third month of therapy, the concentration of apolipoprotein A-I decreased by 15% and the contents of apolipoprotein B and triglycerides increased by 16% and 14%, respectively. These changes the end of the treatment (Table 1, Figs. 1 and 2). The content of LDL CS slightly increased (by 7%) on the sixth month of therapy. Prolonged therapy with obsidan led to an ambiguous dynamics of LPO products in blood plasma in the control patients (Table 1, Fig. 3).

The contents of CD and MDA decreased significantly (by 32% and 22%, respectively) over the first 2 months of obsidan therapy. However, their concentrations increased and approached the initial levels during further therapy. Such changes in blood contents of LPO products indicate the activation of free-radical LPO. This is probably due to the increase in the concentrations of oxidation substrates (triglycerides and LDL CS) [2,13] and the decrease in concentrations of HDL CS and apolipoprotein A-I which have nonspecific antioxidant properties [1]. Positive correlation between CD and MDA concentrations and the content of apolipoprotein B (0.71 and 0.64, respectively) and negative correlation between CD and MDA concentrations and the contents of HDL CS (-0.68 and -0.70, respectively) and apolipoprotein A-I (-0.62 and —0.58, respectively) confirm this suggestion. The activity of erythrocytic glutathione peroxidase changed to a lesser degree during obsidan therapy. The enzyme activity increased on the third month of treatment and decreased on the fourth month of treatment; on the sixth month, it was lower than the initial level ($p<0.05$). These changes in the metabolism of lipids during obsidan therapy are proatherogenic and undesirable [1,2].

Table 1 and Figures 1 and 2 show the content of lipoproteins and the dynamics of LPO indices in the blood of patients with atherosclerosis treated with obsidan and alisat. The contents of HDL CS and apolipoprotein A-I did not change, and the

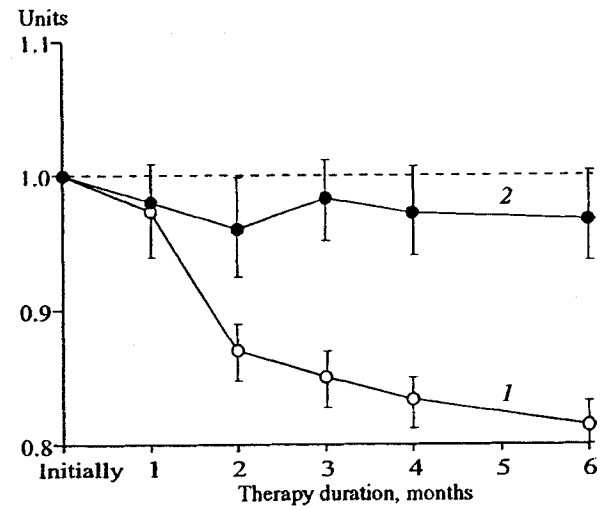

Fig. 1. Blood plasma concentration of high-density lipoprotein cholesterol in patients with atherosclerosis treated with *1*) obsidan and *2*) alisat. Here and in Figs. 2 and 3: mean values before the therapy are taken as one.

TABLE 1. Changes in LPO Parameters and Lipid Concentration in the Blood of Atherosclerotic Patients Treated with Obsidan and Alisat (*M±m*)

Index	Therapy	Initially	Period of observation, months					
			0.5	1	2	3	4	6
CS, mg/dl	Obsidan	285.2±8.7	287.3±10.2	279.7±9.4	283.2±8.8	289.4±9.7	292.6±9.1	296.4±10.7
	Obsidan+Alisat	296.1±10.2	298.3±11.2	291.2±8.9	281.4±9.5	279.2±9.7	280.4±9.2	278.9±10.1
HDL CS, mg/dl	Obsidan	37.1±1.9	37.3±1.1	36.1±1.0	32.5±1.1*	31.6±1.1*	30.9±0.09*	30.2±1.5*
	Obsidan+Alisat	35.9±1.1	36.1±1.1	35.9±0.9	34.8±1.1	35.3±1.2	34.9±1.0	34.7±1.2
LDL CS, mg/dl	Obsidan	209.6±7.4	212.1±10.1	204.1±9.7	208.9±8.7	214.0±8.4	218.4±7.9	222.5±9.6*
	Obsidan+Alisat	216.9±7.6	217.9±8.0	212.0±11.3	204.1±9.7	198.5±11.2	196.7±9.3	192.4±8.9*
Apolipoprotein A-I, mg/dl	Obsidan	96.3±3.9	98.3±3.6	92.4±3.9	91.6±3.7	88.1±3.9*	85.4±3.7*	82.1±3.7*
	Obsidan+Alisat	87.3±3.5	86.1±4.5	89.4±4.1	82.6±4.1	81.0±4.2	84.3±4.0	83.7±4.4
Apolipoprotein B, mg/dl	Obsidan	164.3±9.1	160.0±9.7	168.7±11.2	179.0±8.1*	187.9±10.2*	182.3±9.1*	190.8±11.7*
	Obsidan+Alisat	153.2±19.4	150.6±8.7	154.1±9.0	167.9±8.3	170.2±7.6	175.1±8.4	177.3±9.1*
Triglycerides, mg/dl	Obsidan	192.3±11.7	190.1±10.9	200.3±8.7	208.3±9.4	213.7±10.1*	215.9±9.6*	218.7±9.9*
	Obsidan+Alisat	216.3±10.4	220.4±11.2	218.3±9.9	210.7±10.9	227.1±9.8	244.0±10.0*	249.3±9.5*
CD, U/ml	Obsidan	4.52±0.15	3.34±0.14*	3.06±0.17*	2.80±0.19*	3.81±0.18*	4.09±0.16	4.15±0.18
	Obsidan+Alisat	4.36±0.14	3.06±0.13*	2.41±0.19*	2.51±0.14*	2.59±0.21*	2.93±0.17*	2.85±0.13*
MDA, U/ml	Obsidan	2.93±0.11	2.34±0.12*	2.10±0.13*	1.98±0.10*	2.69±0.12*	2.80±0.17	2.73±0.13
	Obsidan+Alisat	2.61±0.12	1.99±0.13*	1.69±0.19*	1.72±0.13*	1.83±0.14*	1.90±0.16	1.76±0.15*
Glutathione peroxidase,	Obsidan	3.87±0.15	4.0±0.14	4.16±0.13	4.48±0.18*	5.07±0.17*	4.69±0.17*	3.26±0.16*
U activity/g hemoglobin	Obsidan+Alisat	3.54±0.13	3.61±0.16	3.90±0.16	4.39±0.19*	4.56±0.19*	4.68±0.16*	4.78±0.19*

Note. *$p<0.05$ compared with initial values.

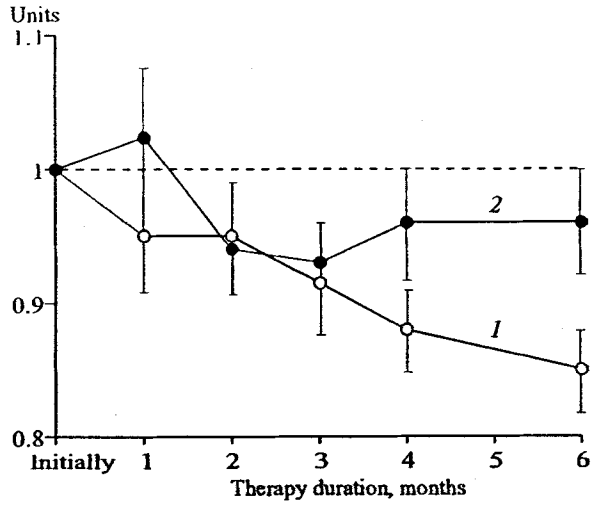

Fig. 2. Blood plasma concentration of apolipoprotein A-I in atherosclerotic patients treated with *1*) obsidan and *2*) obsidan+Alisat.

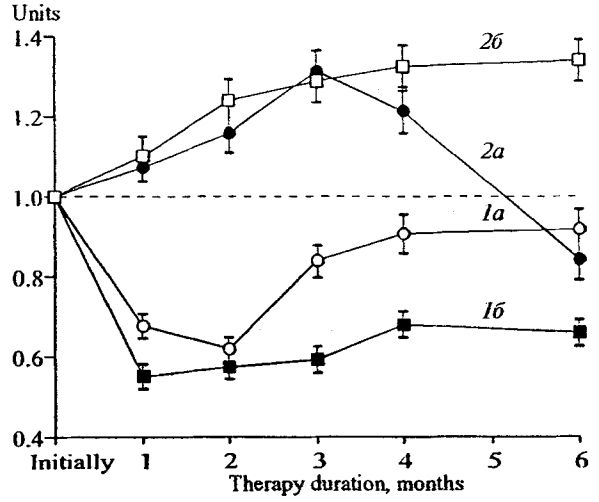

Fig. 3. Blood plasma concentration of *1*) CD and *2*) glutathione peroxidase activity in patients with atherosclerosis treated with *1*) obsidan and *2*) obsidan+Alisat.

concentration of LDL CS decreased by 9% on the sixth month of combined therapy. The contents of triglycerides and apolipoprotein B increased by 15% and 16%, respectively. The content of total CS tended to decrease during combined therapy with alisat and obsidan (Table 1). The concentrations of CD and MDA in the blood of the main group patients decreased during the first two months of combined therapy (Table 1 and Fig. 3) and did not differ from these parameters in the control group patients. Then, plasma concentrations of CD and MDA in the main group patients did not change and were significantly lower those in the control group patients (Fig. 3). The activity of erythrocytic glutathione peroxidase increased during the first three months of combined therapy and did not differ from at during the first three months of obsidan monotherapy ($p<0.05$). However, the glutathione peroxidase activity remained at this level and did not tend to decrease from the fourth to the sixth month of the treatment (opposite to changes in the enzyme activity observed during obsidan monotherapy) (Table 1, Fig. 3). There were no significant correlations between plasma levels of LPO products and lipoproteins during combined therapy.

Thus, prolonged therapy with obsidan leads to atherogenic changes in plasma lipids and activates LPO processes in the blood of patients with atherosclerosis. Combined therapy with obsidan and Alisat allowed us to prevent these metabolic changes. The mechanisms of such effects of alisat are not clear. They are probably associated with the opposite effects of β-adrenoceptor-blocking agents and garlic preparations on the activity of oxymethylglutaryl CoA reductase that controls the biosynthesis of CS [6,16]. Alisat prevents the increase in blood contents of LDL and apoprotein B and, therefore, impedes the increase in the concentration of the LPO substrate and inhibits its free-radical oxidation [15]. This may account for the antioxidant effects of alisat. Our results demonstrate the antiatherogenic activity of Alisat and allow us to recommend this reparation for secondary prevention of atherosclerosis in patients with ischemic heart disease who received prolonged therapy with obsidan.

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