Composition of Energy Metabolism Substrates Increases the Efficiency of Pharmacotherapy of Cardiovascular Diseases

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The substrate composition containing succinic acid, substrates for succinate synthesis, and antioxidants increased the efficiency of pharmacotherapy in patients with coronary heart disease and hypertension. We revealed an increase in the quality of life and decrease in the functional class of heart failure, incidence of arrhythmias and exercise-related pain, and blood cholesterol concentration.

Key Words: *succinic acid; coronary heart disease; hypertension*

The existence of purinergic receptors and signal function of adenyl nucleotides that play a role in intracellular metabolic transformations explains pharmacological efficiency of low doses of purine preparations [6] and other metabolites. Dual function of metabolites provides rapid and simultaneous activation (or change in activity) of physiological reactions upon treatment with low doses of the substance. At the metabolic level, these physiological reactions are initiated with millimolar concentrations of the same substances. Bearing in mind similar final effect of signal and substrate actions of energy metabolism products, we can assume that new medicinal preparations containing micromolar concentrations of substrates can be synthesized according to the general biochemical principles. For instance, antihypoxic effects were observed after treatment with low nonsubstrate doses of succinate as a component of food additives with consideration of predominant oxidation of succinic acid during hypoxia, when oxidation of NAD-dependent substrates yields primarily succinic acid [3,5]. Succinate probably play a signal role. This hypothesis was supported by published data on the interaction of orphan receptors with succinic and α-ketoglutaric acids [8].

Substrate composition Kardiobalans (KB) is a cardiotropic antihypoxic preparation. In our clinical placebo-controlled trial KB was used in combination with basic pharmacotherapy in patients with cardiovascular diseases accompanied by myocardial ischemia.

MATERIALS AND METHODS

KB contains succinate potassium salt (substrate, which can be oxidized during hypoxia), magnesium and sodium salts of aspartate, glutamate, and fumarate (metabolites converted into succinate during hypoxia and anoxia [3]), taurine, and tartarate. KB was administered in combination with basic pharmacotherapy according to the standard therapeutic protocol.

We examined 60 patients (43 men and 17 women, 22-81 years) with coronary heart disease and functional class II-III angina pectoris (coronary heart disease, CHD, *n*=36), stage I-II hypertension (HT, *n*=18), and moderate-to-severe acute myocardial infarction (7-10 days, *n*=6). They were randomly divided into the main (*n*=40) and control group (*n*=20). Each group was divided into equal subgroups 1 and 2. The patients of main subgroups 1 and 2 received KB in doses of 350 and 525 mg, respectively, twice a day.

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TABLE 1. Quality-of-Life Index in Patients with Heart Failure after KB Treatment (n=20, Points, $M\pm m$)

Group	Baseline level	After therapy
Control	6.65±0.79	7.40±0.97
Main group 1	5.60±1.41	7.65±1.02*
Main group 2	5.75±1.08	7.55±0.61*

Note. *p<0.05 compared to baseline level.

The patients of control subgroups received placebo in the corresponding doses. The course of treatment lasted 14 days.

The state of patients was estimated by the condition—activity—mood (CAM) test, quality-of-life index, degree of actual and individual anxiety [1,2], functional class of heart failure (NYHA activity scale) [7], and severity of encephalopathy (number connection test) [9]. Function of autonomic regulation was characterized by cardiointervalography (CIG) on a Valenta diagnostic device. The concentrations of total cholesterol, its atherogenic fraction A-cholesterol, triglycerides, β-lipoproteins, low-density lipoproteins, and very-low-density lipoproteins and activities of lactate dehydrogenase, creatine phosphokinase, alanine transaminase, and aspartate transaminase in the peripheral blood were measured on Hitachi and Spektr analyzers.

The results were analyzed by means of Statistica 6.0 software. The data are expressed as arithmetic means and standard deviations.

RESULTS

Combined use of basic pharmacotherapy and substrate composition KB increased the quality of life in patients with heart failure. This effect did not depend on the dose of KB (Table 1). Combined therapy with KB increased quality-of-life index and in 25% patients decreased functional class of heart failure from class III to class II. In the placebo group this shift was observed only in 1 of 8 patients. Our findings suggest that KB increases locomotor activity and ability to work. We revealed no dose-depend effect of KB.

The CAM test showed that KB does not modulate the subjective evaluation of the state of health in patients. However, many patients reported a decrease in the severity and incidence of exercise-related heart pain, reduction of edema, and increase in daytime diuresis. The Spielberg—Hanin test failed to find changes in the degree of anxiety. The number connection test revealed a positive effect of basic pharmacotherapy (independently on KB treatment). Over 10-day therapy the time of test performance decreased in patients of the main (from 44.5±10.0 to 40.9±9.5 sec, p=0.05) and control group (from 49.8±12.5 to 40.9±9.3 sec, p=0.05).

The study by means of CIG showed that KB treatment significantly decreased dispersion of *R-R* intervals (alleviation of arrhythmia-associated symptoms) and increased the coefficient of monotony (Table 2). I. R. Saakyan revealed a similar, but less pronounced antiarrhythmic effect of Yantavit (succinic acid and

TABLE 2. Parameters of CIG in Patients with CHD after KB Treatment ($M\pm m$)

Subgroup	Baseline level	Day 7 of therapy	After therapy
R—R dispersion, msec^2			
KB (n=11)	1397±92	1213±109	1014±86*+
Placebo (n=7)	1408±125	1451±143	1390±141
Coefficient of monotony, U			
KB (n=11)	207±34	188±41	241±39
Placebo (n=7)	202±50	231±46	211±43

Note. p<0.05: *compared to placebo; +compared to baseline level.

TABLE 3. Plasma Cholesterol Concentration (mmol/liter, $M\pm m$)

Subgroup		Baseline level	Day 7 of therapy	After therapy
Total cholesterol	Main	4.42±1.14	4.04±0.86*	4.06±1.05*
	Control	4.48±1.31	4.42±1.01*	4.64±1.25*
A-cholesterol	Main	1.21±0.28	1.10±0.15*	1.13±0.18*
	Control	1.14±0.19	1.16±0.14*	1.20±0.19*

Note. *p<0.05 compared to baseline level.

glucose) in patients with CHD [5]. The effect of KB did not depend on its dose. In none patients BP elevation (due to binding of substrates to orphan receptors) was observed.

The concentrations of total cholesterol and A-cholesterol in peripheral blood plasma decreased after 1-week treatment with KB (Table 3). Triglyceride concentration tended to decrease. The test preparation had no effect on plasma enzyme activities.

Our results suggest that 2-week treatment with the substrate composition KB increased the efficiency of basic pharmacotherapy in patients with CHD. We revealed an increase in the quality of life and decrease in functional class of heart failure, dispersion of *R-R* intervals, and peripheral blood cholesterol concentration.

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