Clinical and Economic Substantiation of Technologies of Regulation of Energy Metabolism from the Viewpoint of Systemic Pharmacodynamics

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The data of experimental and clinical evaluation and the results of pharmacoeconomic analysis of the effects of regulators of energy metabolism attest to their multiple pharmacodynamics during correction of pathological processes in systems differing by their structure, function, and metabolism. Polyorgan energy protection of regulators of energy metabolism improves organism's resistance, accelerates sanogenesis, and reduces the costs per unit of clinically significant effect. Here we discuss the creation of pharmacotherapeutic technologies based on principles of bioenergetic pharmacology.

Key Words: *regulators of energy metabolism; factor analysis; clinical and pharmacoeconomic effects*

Efforts of classical pharmacology are traditionally aimed at the search for preparations correcting certain pathogenetic elements and at the development of "pathogenetic schemes" of pharmacotherapy of various diseases. Dysregulation of functions, accumulation of entropy, and development of energy deficiency are considered to be typical pathological processes [5]. Most drugs are xenobiotics; they can draw away considerable energy resources of the organism for their biotransformation and elimination and can disturb the function of cell energy-producing systems. This can complicate treatment and delay sanogenesis.

In healthy organism, energy processes are balanced according to demands for optimal functioning of organs and systems. Optimization of utilization of energy resources in the organism and regulation of their supply and distribution in favor of most needing tissues and organsis are a way for natural (not xenobiotic) counteraction of entropy and dysregulation promoting recovery of functions and convalescence. Systemic approach to multidimensional energy protection was realized in the form of pharmacological construction of regulators of energy metabolism (REM) [11-14]. The idea of a new class of drugs containing low doses of energy substrates is based on the concept on homeostatic role of mitochondria and principles of bioenergetic pharmacology [4,16]. The pathological process can be thus alleviated via correction of functions of cell energy-producing systems under conditions of energy deficiency [16]. Here we present the results of systemic analysis of clinical and pharmacoeconomic efficiency of REM during treatment of some prevalent diseases as a prerequisite for the creation of new medical technologies characterized by high efficiency and low costs of treatment.

MATERIALS AND METHODS

Systemic approach to evaluation of the effects of REM was realized though step-by-step clinical and economic analysis of the results of randomized

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clinical trials. Multiplicity of REM pharmacodynamics within one nosological entity was studied in case of CHD associated with arterial hypertension. We used clinical, pharmacological, and economic data grouped in matrices containing informative reporter parameters before and after treatment taken from case reports of patients enrolled in these trials. Clinical evaluation of the effects of REM (amber-cardio phyto) was performed by expert cardiologists of Institute of Pharmacology, Tomsk Research Center O. Yu. Trifonova, Doctor of Science, and V. V. Michailenko, Candidate of Science.

The efficiency of REM under conditions of heterogeneity of the initial information was analyzed after systemic review [1,2,10] of published results of evaluation of clinical and sanitary effects of REM during correction of pathological states of various localization and severity [11-14]: tuberculosis of the lungs, ixodid tick-borne borreliosis with chronic opisthorchiasis, chronic occupational lung diseases, vibration disease, benign hyperplasia of the prostate, chronic prostatitis and erectile dysfunction, CHD with arterial hypertension, acute coronary syndrome (reamberin+amber-force), sanitation in gastroduodenal pathologies, osteoarthrosis, resection of the liver, and ischemic stroke.

In clinical studies, preparations of the Amber series (Institute of Pharmacology, Tomsk Research Center) containing "signal" doses of succinic acid were used [12-14]. Reamberin (1.5% solution in substrate doses) was used in critical states during acute coronary syndrome, resection of the liver, and ischemic stroke [9].

Clinical efficiency of routine medical interventions (control groups) and their combinations with REM (main groups) was compared by the frequency of positive outcomes specific for each nosological entity in the form of intermediate points (clinical, laboratory, and instrumental parameters) related to end-points. Standardized parameters of efficiency were calculated from these frequencies: increase in absolute benefit (IAB), number of patients which should be treated in a certain way for obtaining 1 positive outcome (NPT), and odds ratio for positive outcome (OR) [1,2,10]. Clinicoeconomic and pharmacoeconimic analyses were performed by the method of costs—efficiency [2] using the data on clinical results of treatment, reports from economic departments of hospitals, and price-lists of Protek interregional distributor for the corresponding period.

Coefficient CER (cost-efficiency ratio) was calculated [2]:

$$CER=DC/Ef,$$

where, DC is direct costs for drugs (in rubles), Ef is treatment efficiency according to intermediate criteria used in meta-analysis. Efficiency parameters were grouped into arrays with consideration for heterogeneity [1,3,7,15] of responses from organism's systems to agents of pharmacological correction. Multiplicity of the effects of REM was studied by the method of major components by the factor structure of correlation matrices [3,7] after reduction of their dimension to 2 factors (F_1 and F_2) absorbing more than 50% of overall information. Multidimensional step-by-step analysis of clinical and pharmacoeconomic data was carried out using Principal components & Classification analysis modules of STATISTICA 6.0 software [10].

RESULTS

Systemic analysis of pharmacodynamic interaction of REM with traditional pharmacotherapy on the bases of heterogeneous data for a single nosological entity is presented for CHD associated with arterial hypertension. In the compared groups (each included 25 patients), the general state of patient's health and clinical, pharmacological, and economic parameters of treatment were evaluated before and after treatment by many clinical and pharmacoeconomic parameters (Fig. 1). Additional administration of REM led to clinically and statistically significant increase in treatment efficiency (Fig. 1, *a*), while costs of attaining a unit of clinical effect in the group of energy protection decreased by 1.7-2.0 times (Fig. 1, *b*). Reduction of the dimension of data by the method of major components allowed us to compress information to 3 latent variables absorbing 72% overall dispersion, the first two of them (F_1+F_2) describe 64% variability. For evaluation of possible effects of false correlations, all cells (values of parameters) in the matrices were filled using a random-number generator and the major components were separated. The obtained F_1 and F_2 described only 12.7% of the overall dispersion. As a result of this, informativity of the parameters in statistical modeling was very low and factor load of the major components did not attain the lower reliability limit (0.5).

In contrast, the treatment process and additional energy protection were potent factors structuring the multiple correlation matrix constructed on the basis of actual data. Two latent variables F_1 and F_2 described heterogeneous formalized objects (patients of compared groups) depending on the efficiency of treatment.

The majority of reporter parameters in the real data massif formed information clusters with high factor loads and projections on F_1 and F_2>>0.5. In accordance with this, the addition of REM to the

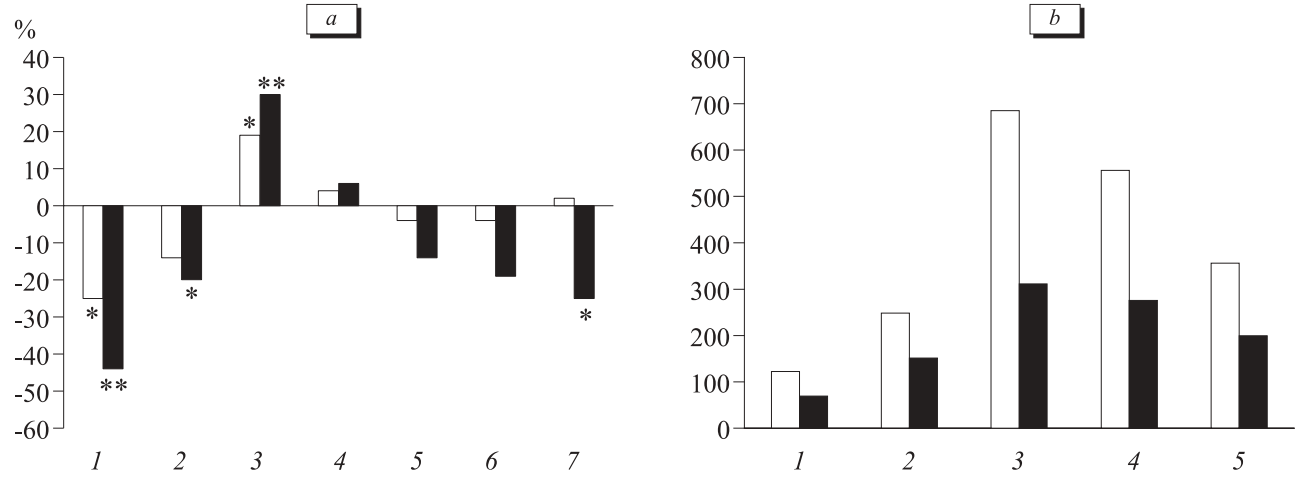

Fig. 1. Clinical and pharmacoeconomic effects of REM in complex pharmacotherapy of CHD. Light bars: control group, dark bars: main group. *a*: *1*) systolic pressure decrease; *2*) diastolic pressure decrease; *3*) threshold load power; *4*) duration of exercise; *5*) total cholesterol content; *6*) LDL cholesterol; *7*) index of atherogenicity. **p*<0.05, ***p*<0.01 compared to initial values. *b*: *1*) drug costs per course, rubles; *2*) CER to percent of patients with normalization of diastolic pressure; *3*) CER to percent of patients with normalization of systolic pressure; *4*) drug costs for reducing diastolic pressure by 10 mm Hg; *5*) drug costs for reducing systolic pressure by 10 mm Hg.

scheme of pharmacotherapy for CHD led to reliable differentiation of patients by the totality of signs characterizing the efficiency of intervention: clinical (taken from case reports) [8] and pharmacoeconomic (calculated from the costs of the course doses of the drugs). In case of formalized presentation of "conditional patients" described using the random-number generator, there were no differences between groups depending on treatment stage (before/after) and type of pharmacotherapy (Fig. 2, *a*). But on the plot of real F_1 and F_2, the compared groups formed compact community of points formally representing patients depending on the stage (before/after), type, and efficiency of pharmacotherapy (Fig. 2, *b*). According to multidimensional characteristics, objects of the main group were shifted to the range of negative values of F_1 and F_2, which was interpreted as predominance of regulating influences and reduction of treatment costs. Multidimensional factor analysis revealed relationships between the element of the formalized system patient—basic therapy—energy protector, according to which all patients can be classified by the efficiency of intervention. The results of systemic analysis of the effect of REM in a single nosological entity by all heterogeneous information (cli-

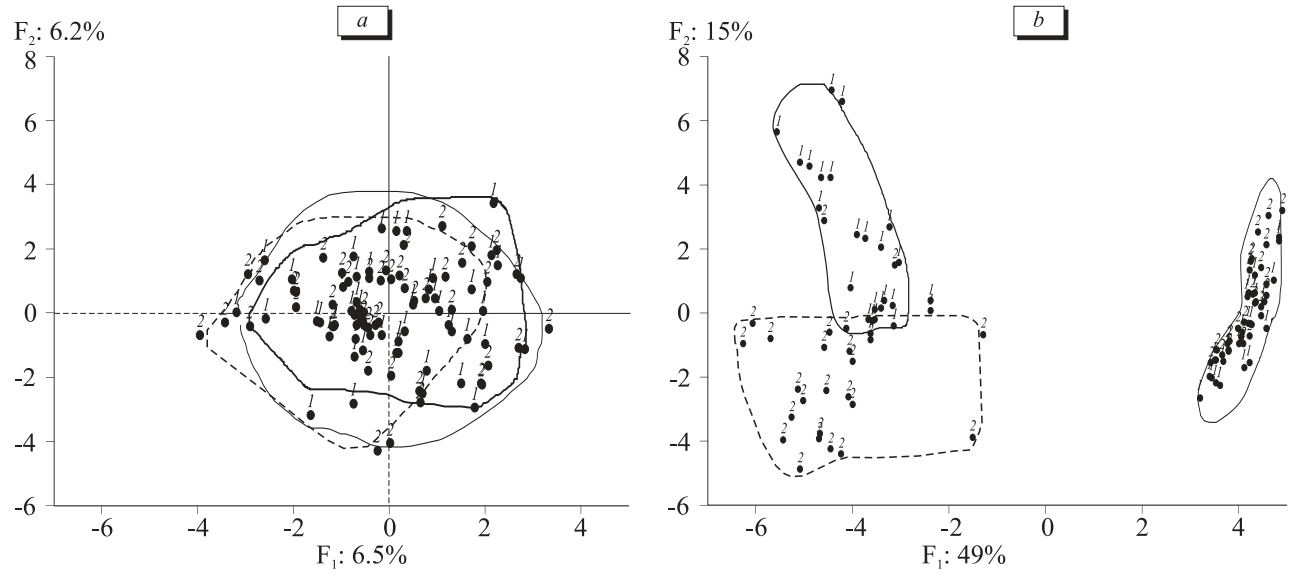

Fig. 2. Multiple character of pharmacodynamic interaction of REM with routine preparations in the therapy of CHD. *a*) statistic model, *b*) actual data. *1*) control group; *2*) main group.

TABLE 1. Clinical and Economic Efficiency of REM in Combination with Routine Drugs

Pathology	IAB (95% confidence interval)	OR (95% confidence interval)	NPT	CER (control group)	CER (main group)	ΔCER, %
Tuberculosis	0.2 [0.3; 0.02]	3.8 [7.0; 2.1]	7	206	125	-40
Ixodid tick-borne borreliosis	0.3 [0.5; 0.03]	3.6 [6.8; 1.9]	4	149	97	-35
Chronic lung diseases	0.2 [0.4; 0.05]	4.0 [5.5; 1.7]	5	86	64	-25
Vibration disease	0.6 [0.8; 0.40]	3.0 [4.0; 1.4]	2	84	57	-32
Prostatic adenoma	0.2 [0.4; 0.04]	2.5 [3.0; 1.1]	4	18	13	-28
CHD	0.2 [0.4; 0.04]	2.2 [3.5; 1.3]	5	122	69	-68
Acute coronary syndrome	0.2 [0.3; 0.04]	2.0 [3.0; 1.1]	5	160	120	-25
Acute coronary syndrome (reamberin)	0.5 [0.6; 0.27]	2.2 [3.5; 1.3]	2	160	60	-63
Resection of the liver (reamberin)	0.6 [0.8; 0.44]	3.2 [6.0; 1.8]	2	2306	89	-96
Ischemic stroke (reamberin)	0.3 [0.5; 0.11]	3.8 [8.4; 2.1]	3	78	39	-50

nical, pharmacological, and economic data) attest to multiplicity of beneficial manifestations of synergistic pharmacodynamic interaction of energy protectors with traditional drugs.

Purposeful evaluation of the effect of REM in pathological process of different localization of severity requires high heterogeneity of the initial data [1,15,17]. This required systematic review of published reports of clinical trials with subsequent meta-analysis of formalized parameters of clinical and pharmacoeconomic efficiency accepted in evidence-based medicine [1,10]. Frequency characteristics of positive clinical outcomes in the main groups were always higher than in the control groups (routine treatment), which resulted from pharmacodynamic interaction of energy protectors with routine drugs. Hence, according to the continuum of formalized qualitative parameters calculated on the basis of frequency characteristics IAB, OR, and NPT, the systemic pharmacodynamic effect of REM consists in improvement of clinical efficiency of traditional schemes of pharmacotherapy of the studied diseases and attests to economic appropriateness of the use of adjuvant energy protection (Table 1).

An obligatory condition for the proven efficiency of new medical intervention is the interrelation of clinical and statistical significance of positive outcomes evaluated by 95% confidence intervals for IAB and OR [1,10]. In our studies IAB in the majority of clinical studies included in meta-analysis was equal or surpassed 0.2, while 95% confidence intervals did not attain zero values. In case of additional treatment with REM, OR was also above the line corresponding to zero effect and was characterized by the position of 95% confidence interval above 1 (logarithmic scale). Thus, meta-analysis of heterogeneous data with due account for inter- and intragroup variability of the frequency reporter-parameters revealed clinical and statistical significance of multiple effects of REM. Wide spectrum of pathological states amenable to correction with REM confirms nonspecific polyorgan type of pharmacodynamic of the new class of preparations.

REM on the basis of mitochondrial substrates are cheap energotropic metabolite-type preparations affecting not only clinical, but also economic parameters of medical interventions. The costs for attaining a unit of clinically significant effect (CER) in the main groups were lower by more than 25%, irrespectively of the pathology, despite the fact that direct costs for complex medical service considerably varied in different diseases (Table 2) primarily due to its different volume and conditions (outpatient department or hospital). In spite of data heterogeneity we can distinguish several typical situations. In case of fixed observation period, the costs of one bed day are similar in parallel groups, while the costs of drugs are insignificantly higher due to additional treatment with REM. In other cases, the costs for drugs as well as the total costs for medical service decrease despite similar terms of observation. The time of stay in the hospital for patients receiving REM can decrease, which leads to a decrease in total costs for bed day, drugs, and the total treatment costs.

Hence, the increase in clinical efficiency of schemes of pharmacotherapy and sanitation in case of REM treatment either little affected the total treatment costs or reduces it due to the decrease in the length of hospital stay and/or drug costs. Comparison of medical service cost increment in case of introduction of REM into the scheme of pharmacotherapy (2-15%) and the range of CER reduction reflecting the decrease of specific costs with con-

TABLE 2. Effect of REM on Economic Characteristics of Medical Intervention (Average Data for One Patient)

Pathology	Treatment duration, days		Overall bed day costs, rubles		Total drug costs, rubles		Total costs of complex medical service, rubles	
	control group	main group	control group	main group	control group	main group	control group	main group
Tuberculosis	90	90	34,200	34,200	4536	4632	38,736	38,832
Ixodid tick-borne borreliosis	22	19	8250	7125	1338	1472	9588	8597
Chronic lung diseases	20	20	5360	5360	292	241	5652	5601
Vibration disease	18	17	4086	3859	292	258	4378	4117
Prostatic adenoma	30	30	0	0	882	948	882	948
CHD	28	28	14,700	14,700	336	211	15,036	14,911
Acute coronary syndrome	24	20	5952	4960	479	346	6431	5306
Acute coronary syndrome (reamberin)	24	20	5952	4960	479	577	6431	5537
Sanitation of children	21	21	5292	5314.3	0	0	5292	5314.3
Sanitation in gastroduodenal pathology	16	16	12,000	12,000	0	0	12,000	12,053
Sanitation in osteoarthrosis	16	16	12,000	12,000	0	0	12,000	12,053
Resection of the liver (reamberin)	6/23*	4/20*	15 415	12,152	9226	6024	24 641	18,176
Ischemic stroke (reamberin)	6/23*	5/18*	37,309	32,688	3054	2738	40,363	35,426

Note. * Mean length of stay in intensive care unit (numerator) and in the department of the corresponding profile (denominator), costs for drugs and medical service were summed up.

sideration for clinical efficiency of the new intervention demonstrates economic benefit of energy protection. Additional costs for adding REM to pharmacotherapy are many times absorbed by the decrease in costs—efficiency coefficient calculated with consideration for costs for drugs and complex medical service. Hence, the use of REM as adjuvant energy protectors can increase economic efficiency of medical intervention and meets the requirements for dominating alternative [1,2] to traditional schemes of pharmacotherapy of prevalent diseases.

Homeostatic role of mitochondria in tissues of visceral organs can be studied only on biopsy material, but the availability and quality of this material are limited due to ethical and technical reasons. Mutual coordination of mitochondrial activity in internal organs (liver, heart, kidneys) and its variability under the action of adverse factors and pharmacological correction were studied in animal experiments with synchronic evaluation of bioenergetic parameters and subsequent multidimensional analysis [6]. It was found that deenergization and dysregulation were associated with disturbances in mutual coordination and hierarchical orientation of functional activity of organelles. During pharmacological correction of energy metabolism, the systemic character of the protective effects of REM manifests in preserved interrelationships between functional activities of mitochondrial pools in internal organs under the action of adverse factors. For instance, pharmacological protection with amber-antitox preparation preserved hierarchical orientation of mitochondrial activities in internal organs (myocardium>kidney>liver) formalized in the space of multidimensional latent variables similarly to that in intact animals. Thus, REM preserved interorgan interaction of cell energy-producing systems disturbed during exposure to adverse factors. Energy protector under these conditions acts as an exogenous activator of the integral function of mitochondria and increases the adaptive resource of the energy metabolism in the body. Effects of REM are summed up at the mitochondrial level and are the factor preserving and stabilizing systemic interactions of organs and tissues, which provides potentiating pharmacodynamics of energy protectors under various pathological states.

Systemic analysis of clinical and pharmacoeconomic data shows that REM added to traditional schemes of pharmacotherapy form a common vector of beneficial effect irrespective of the type of pathology. Pharmacological correction of the energy metabolism at the level of mitochondria under pathological states leads to clinically significant increase in treatment efficiency and economic benefit of medi-

cal interventions, which can be attained by using REM-technologies according to the following formula:

REM-technology=routine scheme of pharmacotherapy+REM,

where REM is energy protector containing mitochondrial substrates in signal or substrate doses.

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