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Research Article

The Importance of the Smoking Factor in Personalized Complex Pharmacotherapy of Ischemic Heart Disease with the Use of Metabolic Correctors

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ABSTRACT:
The work is devoted to the study of the significance of the smoking factor in the realization of potentially positive cardiocytoprotective properties of metabolic correctors in the complex therapy of ischemic heart disease (IHD). A randomized study of 160 patients with stable angina pectoris was performed, 60 of them were smoking and 100 of them were non-smoking. The clinical efficiency of the treatment was assessed by the integral index of the treatment effectiveness coefficient in percent (Cte,%). The individual effectiveness of metabolic correctors was evaluated in in vitro samples on blood leukocytes of patients using the DNA comet method. The subject of the study were trimetazidine, meldonium, phosphocreatine. A significant decrease in the clinical efficiency of treatment of smokers (Cte = 28.14 ± 4.10%) was found in comparison with non-smokers (Cte = 37.94 ± 2.42%, p = 0.03). Testing of metabolic correctors in vitro showed the appearance of genotoxic properties in trimetazidine, meldonium and phosphocreatine when administered to smokers with IHD. It was found out prognostic inefficiency and inexpediency of metabolic drugs including in the complex pharmacotherapy of ischemic heart disease in smokers. The results of the study indicate the need for a personalized approach to the appointment of cardiac cytoprotectors to patients with IHD, depending on the presence of a smoking factor.

Key words: smoking, ischemic heart disease, personalized pharmacotherapy, metabolic correctors, trimetazidine, meldonium, phosphocreatine.

INTRODUCTION

Ischemic heart disease (IHD) is one of the main causes of death in many countries of the world [1]. There is a different trend in the demographic indicators of mortality from cardiovascular diseases in different European countries: in the West European region - a steady decline in mortality, in the East European - the absence of such a decrease and even the growth of this indicator [2]. The Russian Federation, unfortunately, takes the leading position in Europe in terms of mortality from cardiovascular diseases [3]. Countries that have such a demographic situation are proposed to pay special attention to the correction of cardiovascular disasters risk factors, to study the causes of the low treatment effectiveness [1]. One of the causes of the insufficient effectiveness of the developed standards and recommendations for the treatment of IHD may be the lack of consideration of a complex of individual factors that influence on the outcome of pharmacotherapy. Scientific research in the field of personalization of the prescription of medicines for the treatment of socially significant diseases is a priority in the Russian Federation [4]. The direction of personalized medicine is included in the modern concept of medicine development. President V.V. Putin declared the personalized medicine as one of the strategic directions of scientific and technological development of Russia [5].

The smoking factor is a recognized risk factor for the development of cardiovascular disasters

[6,7,8,9]. According to some authors, the presence of a smoking factor determines the limitation of the clinical efficiency of some antihypertensive and antianginal agents [10,11]. To increase the effectiveness of pharmacotherapy of IHD is recommended additionally to the drugs of basic therapy to prescribe drugs of the metabolic series in order to provide cardiocytoprotection [7,8]. Trimetazidine, meldonium and phosphocreatine in experimental myocardial ischemia exhibit the properties of cardiac cytoprotectors: they help stabilize cardiomyocyte membranes, economize energy in the myocardium, and reduce the degree of hypoxia [12]. Whether the smoking factor is important for the realization of potentially positive cardiocytoprotective properties of metabolic correctors in the complex treatment of patients with ischemic heart disease is not described in literature.

The purpose of this study was to determine the importance of the smoking factor in the individual effectiveness of metabolic correctors in the complex pharmacotherapy of ischemic heart disease.

METHODS

A randomized, open-label, controlled trial was conducted in 160 patients with ischemic heart disease: stable angina pectoris of I-III functional classes at the age of 37 to 81 years (mean age 59.26 ± 0.74 years). In the majority of patients, angina pectoris was combined with hypertension (89.4%), rhythm disturbances (24.4%), post-infarction cardiosclerosis (48.8%), chronic heart failure (94.4%), some with diabetes mellitus II type (23.1%). According to the presence of the smoking factor, the patients were divided into two groups: the 1st group consisted of 60 smoking patients, the 2nd one consisted of 100 non-smoking patients. Patients underwent a comprehensive examination according to the recommendations of the Russian Scientific Society of Cardiology [8]. The examination program included a general blood test, a biochemical blood test, including a lipidogram, electrocardiography (ECG), echocardiography (EchoCG).

Clinical efficiency of the treatment was assessed by standard criteria of angina pectoris functional class reducing, improving the clinical and hemodynamic state of patients, improving the tolerance to physical load with the calculation of the integral coefficient of treatment efficiency in percent (Cte,%) according to our method (Patent of Ukraine No. 58859, 2003). The effectiveness of metabolic correctors was determined by testing drugs in vitro on blood leukocytes of patients with the determination of their potential genotoxicity or genoprotective effect by the method of DNA comets according to the method developed by us [13]. The subject of our study were three drugs from the group of metabolic correctors: trimetazidine, meldonium and phosphocreatine.

The prognostic significance of the smoking factor for the effectiveness of metabolic correctors was determined by the statistical method of Wald's prognostic analysis. Comparative analysis between the groups was carried out by statistical methods with the calculation of arithmetic means and their errors, median and quartiles, with an estimation of the reliability of differences in the Student's t-test and the Mann-Whitney U- test. Statistical processing of data was carried out using the software "Microsoft Excel 2007" and "SPSS for Windows 11.0". To evaluate the results of the study using the DNA comet method, the software "CometScoreTM v.1.5" was used.

RESULTS AND DISCUSSION

To clarify the importance of the smoking factor in personalized pharmacotherapy of ischemic heart disease, a comparative analysis of two groups of patients - smokers and non-smokers - was conducted. A number of significant differences were found out (Table 1 and Table 2).

Table 1. : Comparative analysis of indicators of pathogenetic features and the effectiveness of IHD treatment in smokers and non-smokers

Indicators	Smoker patients, n=60	Non-smoker patients, n=100	Reliability of differences p
Average age, years	55.77±1.15	61.27±0.87	0.001
Height, m	1.73±0.01	1.67±0.01	0.001

Diabetes mellitus: duration in years	0.60±0.31	1.95±0.48	0.019
Systolic blood pressure: mmHg	133.09±2.84	141.11±2.31	0.032
Diastolic blood pressure: mmHg	96.67±4.01	83.07±2.41	0.007
Hemoglobin, g / l	146.76±1.99	138.35±2.51	0.018
Color indicator, units	0.93±0.01	0.89±0.01	0.012
Glycated hemoglobin,%	5.58±0.15	6.19±0.29	0.065
Potassium of blood, mmol / l	4.83±0.08	4.61±0.07	0.047
Cholesterol total, mmol / l	5.01±0.17	5.70±0.16	0.007
Lipoproteins of low density, mmol / l	3.05±0.16	3.56±0.15	0.030
EchoCG: LV EDS, mm	55.51±1.27	51.94±0.96	0.025
EchoCG: LV EDV, ml	151.20±6.77	122.43±4.45	0.001
EchoCG: LV ESS, ml	72.94±5.82	55.91±3.89	0.012
EchoCG: LV EF, %	53.41±1.85	57.78±1.36	0.054
ECG: total voltage R in standard leads, mm	13.18±1.07	18.61±1.31	0.006
Coefficient of treatment efficiency, %	28.14±4.10	37.94±2.42	0.030

Note. The reliability of the differences was assessed according to Student's t-criterion. LV EDS- left ventricular end diastolic size, LV EDV - left ventricular end diastolic volume, LV ESS - left ventricular end sistolic size, LV ESV - left ventricular end sistolic volume; LV EF - left ventricular ejection fraction.

Table 2. Comparative analysis of indicators of pathogenetic featuresand the effectiveness of IHD treatment in smokers and non-smokers

Indicators	Smoker patients, n=60	Non-smoker patients, n=100	Reliability of differences p
Functional class of angina pectoris	2.63/ 3.00 (2.00;3.00)	3.00/ 3.00 (2.00;3.25)	0.028
Diabetes mellitus: severity	0.22/ 0.00 (0.00;0.00)	0.55/ 0.00 (0.00;1.00)	0.086
Evaluation of the effectiveness of treatment: subjective improvement, scores	1.07/ 1.00 (0.50;2.00)	1.51/ 1.00 (1.00;2.00)	0.029
Evaluation of the effectiveness of treatment: objective improvement, scores	0.99/ 1.00 (0.50;2.00)	1.29/ 1.00 (1.00;2.00)	0.075
DNA initial status, DNA comet index	0.38/ 0.10 (0.02;0.67)	0.18/ 0.06 (0.00;0.18)	0.070
DNA: phosphocreatine, the index of DNA comets	0.83/ 0.61 (0.07;1.37)	0.30/ 0.08 (0.00;0.38)	0.004

Note. The numerator is the arithmetic mean, the denominator is the median, 25% and 75% quartile. The reliability of the differences was evaluated according to the Mann-Whitney U-criterion.

The average age of smokers was 55.77±1.15 years, that significantly lower, in comparison with non-smokers 61.27±0.87 (p=0.001). Probably, due to the predominant influence of the age factor in this group of patients, the severity of the underlying disease (angina pectoris), the accompanying pathology (diabetes mellitus) and the lipid profile are more favorable.

Smokers have a higher hemoglobin level and color index, which may indicate smoking as an additional factor of hypoxemia [14]. The objective status of smokers is significantly worse according to echocardiography and electrocardiography: the heart cavities are enlarged, the ejection fraction is lower, the violations of local contractility are more pronounced, the voltage on the ECG is reduced to the level of myocardial dystrophy (Table 1).

According to our study, smokers in the initial status have significantly more damaged DNA compared to non-smokers (Table 2, Figure 1), which indicates on the presence of genotoxicity in components of tobacco smoke, that corresponds to the literature data [15].

The effectiveness of treatment of smoking patients is significantly worse in terms of indicators of subjective and objective improvement of the condition, the integral coefficient of treatment effectiveness. Thus, a significant difference was found between the groups in terms of the subjective improvement index, which in the 1st group was 1.07 / 1.00 (0.50, 2.00), in the 2nd 1.51 / 1.00 (1.00; 2.00) points (p <0.05); By the index of objective improvement of the condition - in the 1st group 0.99 / 1.00 (0.50,

2.00) points, in the 2nd 1.29 / 1.00 (1.00, 2.00) points (p = 0 , 07); by the index of the efficiency of treatment - in the 1st group of Cte was 28.14 ± 4.10%, in the 2nd group 37.94 ± 2.42% (p <0.05). Other researchers also found a significant adverse effect of the smoking factor on the effectiveness of a number of drugs, including nitrates and antihypertensive agents [10,11]. Moreover, an extensive review of the literature on five electronic databases (Medline, PubMed Central, Cochrane library, Pascal and Web of Science), published by Pluvy I., Garrido I., Pauchot J. et al. (2015), showed the determining role of the smoking factor in violation of the healing process of the vascular wall after surgical treatment of coronary vessels, and the authors strongly recommend to patients quit smoking at least 4 weeks prior to surgery and 2 weeks after surgery. [14].

Testing of metabolic correctors in vitro showed unambiguous genotoxicity of the latter in case of their introduction into the blood of smokers. Thus, the introduction of phosphocreatine into the in vitro test of blood leukocytes of smokers leads to even more destruction of the genome, in comparison with non-smokers (Figure 1 and Table 2). Under the influence of trimetazidine in vitro, destruction of DNA was observed in patients who smoke 4.21 ± 1.61 cigarettes per day and DNA repair was observed in patients who smoke 0.41 ± 0.41 cigarettes per day (p <0.05). Under the influence of meldonium, destruction of DNA was observed in patients who smoke 3.94 ± 1.55 cigarettes per day and DNA repair was observed in patients who smoke 0.30 ± 0.30 cigarettes per day (p <0.05). According to the Wald's prognostic analysis, the smoking factor determines the prognostic inefficiency and inexpediency of trimetazidine administration (the prognostic coefficient was minus 7, the coefficient of informative value of the sign was 0.49) and meldonium (the prognostic coefficient was minus 6, the coefficient of informative value of the sign was 0.38).

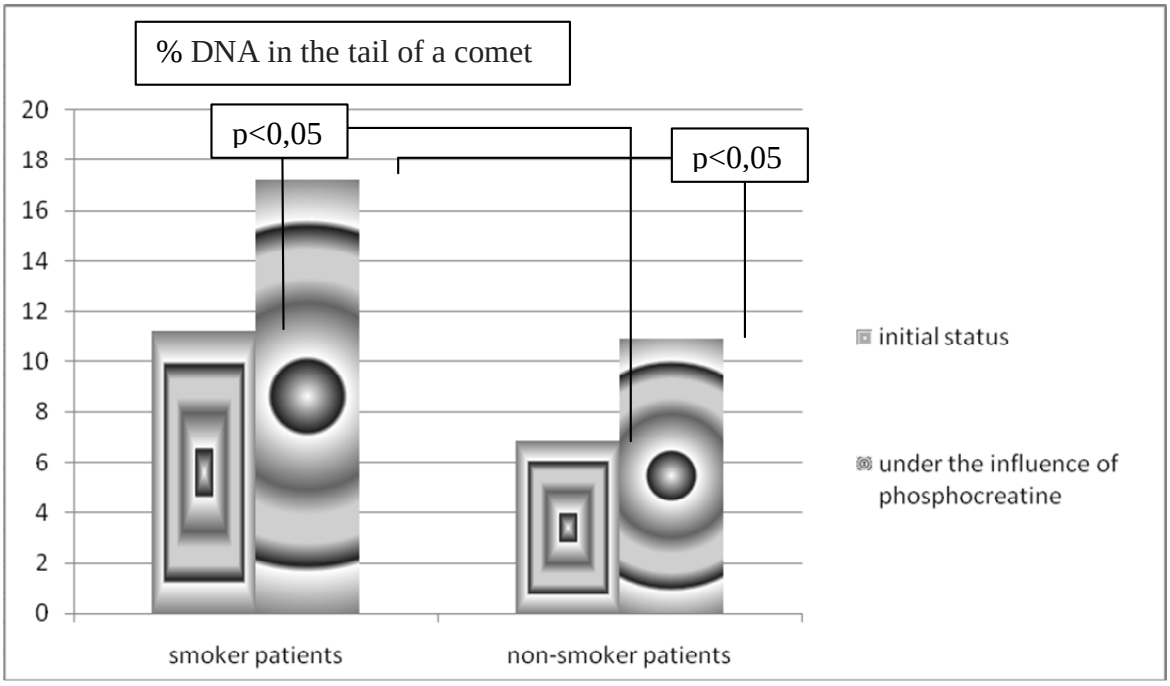

Figure 1. The percentage of DNA in the tail of a comet of blood leukocytes of smokers and non-smokers with IHD in the initial state and when a phosphocreatine is introduced into the sample (in vitro testing)
Note. The reliability of the differences was assessed according to Student's t-criterion

The search for possible causes of the detected prognostic ineffectiveness of metabolic correctors in smoking patients with IHD showed a number of pathogenetic mechanisms for the formation of this phenomenon. Thus, smoking has a widespread and multifactorial effect on the human body [9,14]. Nicotine and tar in tobacco smoke contribute to the development of atherosclerosis by activating the processes of lipid peroxidation and inflammation [4,16]. Reactive oxygen species and hydrogen peroxide are capable to destroy cell membranes and to fragment

DNA [17]. Endothelial dysfunction, hypoxia, immune disorders due to the influence of components of tobacco smoke lead to damage to repair processes at the level of the vascular wall [14,18]. Restriction of the functional adaptive reserve of cells of the vascular wall to restore its resource determines the ineffectiveness of agents that stimulate metabolism [19].

Apparently, the genotoxicity of the components of tobacco smoke creates a certain direction of cellular metabolism in the direction of activation of catabolic processes, and with the introduction of drugs of the metabolic series, these unfavorable processes of destruction of cell membranes and DNA are progressively developed. As biostimulants can not be administered in the presence of a cancer tumor, drugs that activate the metabolism should not be used for the treatment of ischemic heart disease in smoking patients, in order to avoid the stimulation of adverse effects of the components of tobacco smoke.

CONCLUSION

The presence of the smoking factor in patients with ischemic heart disease (stable angina pectoris) determines a significant decrease in the clinical effectiveness of complex treatment and causes prognostic inefficiency and inexpediency of using metabolic correctors as cardiac cytoprotectors due to the formation of their individual genotoxicity in this category of patients. The results of the study indicate the need for a personalized approach to the appointment of cardiac cytoprotectors to patients with IHD, depending on the presence of a smoking factor.

SUMMARY

1. A significant decrease in the clinical efficiency of ischemic heart disease treatment was found in smokers (Cte = 28.14 ± 4.10%) in comparison with non-smokers (Cte = 37.94 ± 2.42%, p = 0.03).
2. Testing of metabolic correctors in vitro showed the appearance of genotoxic properties in trimetazidine, meldonium and phosphocreatine when administered to smokers with IHD.
3. It was found out prognostic inefficiency and inexpediency of metabolic drugs including in the complex pharmacotherapy of ischemic heart disease in smokers.
4. The results of the study indicate the need for a personalized approach to the appointment of cardiac cytoprotectors to patients with IHD, depending on the presence of a smoking factor.

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