THE PLACE OF MELDONIUM IN COMPLEX TREATMENT OF PATIENTS WITH COMORBIDITY OF CHRONIC PANCREATITIS AND STABLE CORONARY HEART DISEASE

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Rezumat. Rolul medicamentului Meldonium în tratamentul complex al pacienților cu pancreatita cronică asociată cu boala coronariană stabilă

Terapia metabolică este una dintre puținele metode de restabilire a funcției normale a tuturor organelor și sistemelor vitale. Scopul studiului a fost de a examina eficacitatea cursului de tratament medicamentos metabolic cu Vazonat (meldonium dihidrat) pentru corectarea dereglărilor prooxidanț-antioxidante și trophologice la pacienții cu patologie combinată: pancreatită cronică (PC) și boala coronariană stabilă (BCS). Studiul a inclus 90 de pacienți cu PC în asociere cu BCS, care au fost divizați în 2 grupuri în funcție de tratament: grupul I, 45 pacienți, au primit tratament convențional (TC); grupul II, 45 pacienți, suplimentar a fost administrat Vazonat: 5 ml intravenos, 10 zile, urmat de administrarea unei capsule (250mg), de 2 ori pe zi, timp de o lună. S-a demonstrat că adăugarea la tratament a medicamentului Vazonat la pacienții cu patologia asociată PC și BCS îmbunătățește indicatorii de stare trophologică și a sistemului antioxidant-prooxidant.

Cuvinte-cheie: pancreatită cronică, boală coronariană stabilă, terapie metabolică, meldonium, Vazonat

Summary

Metabolic therapy is one of few ways to recreate normal work of all vital organs and systems. The aim of the work was to examine the efficiency of protracted treatment with metabolic medication Vazonat (meldonium dihydrate) on the correction of the prooxidant-antioxidant and trophological violation in patients with comorbide course of chronic pancreatitis (CP) and stable coronary artery disease (SCAD). The study included 90 patients with CP and SCAD who were divided into two groups: I group (45 patients) received standard treatment (ST); II group (45 patients) except ST additionally received meldonium according to the following sketch: 5ml intravenously once a day during 10 days with its succeeding receiving of 250 mg twice a day in capsules during one month. It was proved that adding meldonium to the complex treatment of the patients with CP and SCAD comorbidity greatly assists improving of the indices of trophological and prooxidant-antioxidant in comparison with general basic therapy.

Key words: chronic pancreatitis, stable coronary heart disease, metabolic therapy, meldonium, Vazonat

Резюме. Роль медикамента Мельдоний в комплексном лечении больных хроническим панкреатитом, ассоциированным со стабильной ишемической болезнью сердца

Метаболическая терапия – один из немногих способов восстановить нормальную работу всех жизненно важных органов и систем. Цель исследования состояла в изучении эффективности курса лечения метаболическим препаратом Вазонат (дигидрат мелдония) для коррекции прооксидантно-антиоксидантных и трофологических нарушений у пациентов с сочетанной патологией: хроническим панкреатитом (ХП) и стабильной ишемической болезнью сердца (СИБС). Исследование включало 90 пациентов с ХП в сочетании с СИБС, которые были разделены на две группы в зависимости от программы лечения: I группа (45 пациентов) получила традиционное лечение (ТЛ); группа II (45 пациентов), кроме ТЛ, дополнительно получали Вазонит следующим образом: 5мл внутривенно болюсно 1 раз в день в течение 10 дней с последующим приемом 1 капсулы (250 мг), 2 раза в день в течение одного месяца. Было показано, что дополнение лечения пациентов с ХП в сочетании с СИБС препаратом

Вазонат способствует улучшению показателей трофологического статуса и прооксидантно-антиоксидантной системы, чем стандартная базовая терапия.

Ключевые слова: хронический панкреатит, стабильная ишемическая болезнь сердца, метаболическая терапия, мельдониум, Вазонат

Background. CP is one of the most common, rapidly progressive pancreas diseases (increase up to 70.0%) with high cases of temporary incapacity to work and primary invalidity (to 15.0%). CP is characterized by a progressive course with the growing of functional insufficiency of the pancreas, development of trophological insufficiency (TI) and abnormalities in the prooxidant-antioxidant system [1,2,3]. Such epidemiological data are largely derived from the maintenance of the significance of the following main etiological factors of CP: alcohol abuse, presence of the liver and biliary tract diseases, stomach and duodenum diseases, hyperlipidemia which is an atherosclerosis component, and also the increase of the influence of the adverse environmental factors [4,5,6].

CP causes imbalance between the intake of nutrients in the patient's body and his need in them. Under these conditions TI, which is characterized by the syndrome of energy, protein, vitamins, minerals and electrolytes deficiency, especially protein deficiency, secondary immunodeficiency, osteoporotic symptoms, anemia, etc., deepens [7, 8, 9]. In the setting of progressive functional insufficiency of the pancreas and TI enhancement, the reserves of the nutrients in tissues run out; this initially leads to biochemical and functional changes, and subsequently is manifested in numerous and complex clinical symptoms [10,11]. The TI development contributes to the CP progression as well as its complications. Affected by the formed TI, there appears a deficiency in microelements and vitamins, which is an underlying decrease of the antioxidant system (AOS) function with CP and lipid pre-oxidant (LPO) activation, chronic inflammatory process in the pancreas tissue is potentiated, which leads to the progression of fibrosis and atrophy of the parenchyma [12,13].

The activation of the LPO with the simultaneous development of AOS insufficiency occurs in the patients with the comorbid course of CP and SCAD. Thus, the imbalance in the LPO/AOS system is a damaging link in the chain of a metabolic control; it affects the formation and the progression of CP. Besides, the presence and depth of the disturbances in the prooxidant-antioxidant system largely determine the severity of the disease. During oxidative stress free radicals block metabolism in acinar cells, melt lysosome zymogen granules, oxidize lipids of cell membranes, thus an inflammatory reaction with mast cells degeneration, platelets and complement activation begin, which in turn activates pancreatic proenzymes [14,15].

It is known that CP negatively affects cardiovascular system. It has been found that 15.5% of patients with gastroenterological abnormalities, including pancreatitis, have got SCAD. The mechanisms of the impact of implementation of inflammatory process in the pancreas on the development and progression of SCAD have not been explored sufficiently so far [16]. The combination of CP and SCAD leads to a number of structural and metabolic changes that affect the course of the both diseases, and causes the necessity of the development of a systematic approach to the study of the indicated disorders in this group of patients [17]. The uncertainty of these mechanisms leaves the issue of the drug therapy of such patients unsolved, that generally reduces the effectiveness of the treatment of the patients suffering from SCAD. Therefore, the search for effective treatment regimens in this area is essential for modern medicine [18, 19].

The standard basic comorbidity therapy of CP and SCAD does not include correction of trophological and prooxidant-antioxidant disorders [20]. The prescription of metabolic drugs has become common in medical practice in the recent years. Vazonat, 'Onlinefarm', Latvia, (meldonium dehydrate) is one of the most affordable and the main high-tech metabolic cytoprotector. Vazonat belongs to the partial fatty acid oxidation inhibitors. The mechanism of meldonium action is linked to the return limit of speed of biosynthesis of carnitine with its predecessor – gramma-butyrobetaine. Consequently, carnitine mediated transport of long-chain fatty acids across mitochondrial membranes, without affecting the metabolism of short-fatty acids, slows down, that is why Vazonat is able to influence the changes in trophological and prooxidant-antioxidant statues.

So, the use of metabolic drugs in a standard basic treatment of comorbidity CP and SCAD is the most appropriate and pathogenically reasonable.

The purpose of the research was to investigate the effectiveness of a course of treatment with metabolic drug Vazonat (meldonium dihydrate) to the correction of trophological and prooxidant-antioxidant disorders in the patients with comorbid course of CP and SCAD.

Materials and methods. In order to achieve our aim, we selected 90 patients with CP concomitant

with SCAD (I-II functional classes of angina of pectoris), who were treated at the day patient department at Ternopil City Municipal Hospital № 2. The groups consisted of 46 men (51.2 %), the overall average age – (49.9±8,7) years old and 44 women (48.8 %), the overall average age – (52.65±6.2) years old. The study did not include patients with acute forms of IHD in amnesia, insulin-dependent diabetes, unstable angina, severe hypertension, severe cardiac arrhythmias and severe comorbidities.

Depending on the treatment programs for patients, they were divided into two groups; I group (45 patients) received the standard treatment (ST) (nitrates, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists II, calcium channel blockers, statins, antiaggregants, antispasmodics, prokinetics, proton pump inhibitors, enzyme preparations); II group (45 patients) except for ST received additional drug Vazonat (meldonium dihydrate) as follows: 5 ml intravenous bolus injection once a day for 10 days followed by 1 capsule (250 mg), two times per day for one month. The control group consisted of 20 healthy individuals aged from 19 to 46 years old, the overall average age – (32.2±1,8) years old. There were 11 men and 9 women among them, 55% and 45% respectively.

The state of POL and AOS before and after treatment was estimated according to the levels of malonic aldehyde (MA), superoxide dismutase (SOD), SH-groups, catalase and caeruloplasmin.

SOD activity was determined on the basis of its ability to compete with nitrotetrazolium blue for superoxide anions, which are formed by the interaction of the reduced form of aerobic NADN2 and phenazine methosulfate. The amount of the enzyme was determined by spectrometric method. The amount of (62.15±2.82) units is considered to be the norm.

The level of catalase activity was determined by the ability of hydrogen peroxide to form a stable colored complex with ammonium molybdate, the intensity of the color depends on the catalase activity in the sample. The norm of catalase activity in blood is (17.48±0.87) %.

The levels of SH-groups, ceruloplasmin and MA were determined by Boyer, H.D. Ravin and V.N. Orehovych's methods with tiobarbiturat acid respectively. The norm of SH-groups in blood is – (60.5±2.13) mmol/L, MA – (2.810±0.085) mcmol/L, ceruloplasmin – 300 mg/l.

To evaluate the trophological status before and after the treatment of CP in combination with SCAD we used the definition of such indicators as: hemoglobin (Hb), erythrocytes (Er), total protein (TP), serum transferrin (TS) and serum ferritin (FS).

Hb level was determined by photometric method, the number of Er in the blood – by routine method. The norm is considered to be at least 120 g/l for men and 110 g/l for women and 4.0 – 5.0×10^{12}/l for men and 3.7 – 4.7×10^{12}/l for women respectively. TP in blood was determined by the conventional method, the norm of which is – 65 – 85 g/l. Normal amounts of FS and TS in serum are: 10.0 – 147.0 ng/ml – for women and 22.0 – 346.0 ng/ml – for men and 215.0 – 380.0 mg/dl for women and men respectively.

Statistical significance of differences was assessed by averages Mann – Whitney-criteria ($p<0.05$).

Results and discussion. In the course of studying the syndrome indicators of LPO and AOS before the treatment, the patients with CP combined with SCAD had MA level, as a marker of intensification of lipid peroxidation, significantly higher in the I and II study groups compared with the control and they were respectively (6.35±0.07) mcmol/l and (6.39±0,09) mcmol/l. After the treatment MA level in I group significantly decreased by 1.40 mcmol/l (22.05 %), while in II group this date significantly decreased by 2.22 mcmol/l (34.75 %). Such changes point to a more significant inhibition of oxidative mechanisms under the influence of meldonium (Vazonat) compared with the results of traditional treatment (table 1).

Also, before the treatment we noted a significant decrease in enzyme activity of AOS by levels of SOD (I group – (39.22±0.47) units, II group – (39.27±0.45) units) and SH-groups (I group – (38.55±0.47) mmol/l; II group – (38.52±0.45) mmol/l) in both study groups compared to the control. After the provided treatment we observed a more considerably significant increase of SOD activity (by 24.98 %) and the increase of SH-groups (by 15.81 %) in the II group, while in the I group, these data increased slightly and unreliably.

The level of catalase in serum before the treatment in I and II groups of patients was significantly higher compared to control ((55.72±1.12) % and (55.77±1.03) % respectively). After the treatment, this indicator significantly decreased by 16.22 % in the I group and by 30.68 % in the II group that again proved the antioxidant properties of the drug Vazonat (meldonium dihydrate). Regarding the ceruloplasmin of blood in the I and II groups, this indicator was increased compared to control; after the treatment the level of ceruloplasmin in the two study groups significantly decreased (by 13.18 % in the I group and by 23.48 % in the II group) (Image 1).

Table 1

Status of indicators of LPO/AOS in patients with CP concomitant with SCAD before and after treatment in two comparative groups

Indicator	Control (n=20)	I group (n=45)		II group (n=45)	
		Before treatment	After treatment	Before treatment	After treatment
MA, mcmol/l	2.180±0.09	6.35±0.07 *p<0.001	4.95±0.12 **p<0.01	6.39±0.09 *p<0,001	4.17±0.15 **p<0.001 ***p<0.001
SH-groups, mmol/l	68.50±2.13	38.55±0.47 *p<0.001	40.33±0.84 **p>0.05	38.52±0.45 *p<0.001	44.61±0.22 **p<0.01 ***p<0.05
SOD, units	62.15±2.85	39.22±0.47 *p<0,001	42.37±0.53 **p>0.05	39.52±0.45 *p<0,001	49.39±0.31 **p<0.01 ***p<0.05
Catalase, %	17.48±0.87	55.72±1.12 *p<0.001	46.69±0.41 **p<0.01	55.77±1.03 *p<0.001	38.66±0.32 **p<0.001 ***p<0.01
Ceruloplasmin, mg/l	245.60±2.61	591.12±6.08 *p<0.001	512.02±5.96 **p>0.05	593.08±5.01 *p<0.001	453.81±5.01 **p<0.01 ***p>0.05

Notes:
* probability of difference regarding to such indicators of control;
** probability of difference regarding to such indicators of their patients with CP+SCAD before treatment;
*** probability of difference regarding to such indicators of patients in I group.

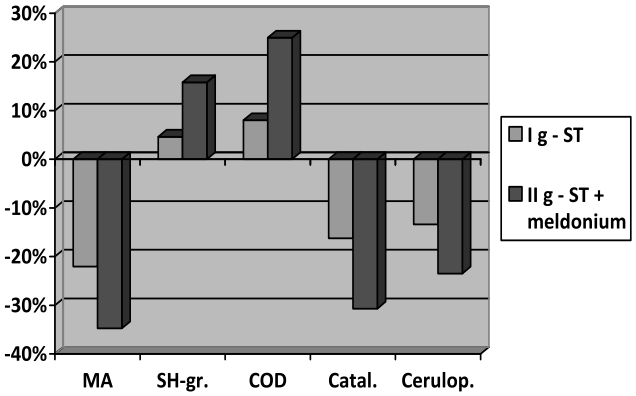

Image 1. *Changes indicators of LPO/AOS after treatment in patients with CP concomitant with SCAD in two comparative groups*

Based on the data presented in table 2, we can state high efficiency of the proposed treatment regimen that is enhanced by using meldonium compared to conventional therapy. TP level in blood after the treatment in I group grew by 3.41 g/l – 5.4 %; in II group – by 7.90 g/l – 13.8 %, that is by 8.4 % higher compared to this indicator in the I group. Also, we established a significant increase of Hb level in I group from (101.17±1.87) g/l to (107.58±1.28) g/l and increase of Er level in blood (8.48 %), while in II group there was a significant increase of both the level of Hb from (100.64±0.55) g/l to (118.38±1.23) g/l, and the level of Er in blood by 19.69 %.

The higher efficiency of the treatment regimen that is enhanced by using meldonium, in patients with CP combined with SCAD can also be judged by levels of TS and FS. TS level before treatment in I group was – (532,22±16,17) g/l, in II group – (527,99±19,72) g/l. After the treatment, the indicator fell by 8.71 % in I group and by 15.11 % in II group. The improvement of FS level in I and II groups (by 17.72 % and by 35.45 % respectively) was noted, but the growth of this indicator in II group was more significant that underlines the importance of metabolic therapy in patients with comorbidity course of CP and SCAD (Image 2).

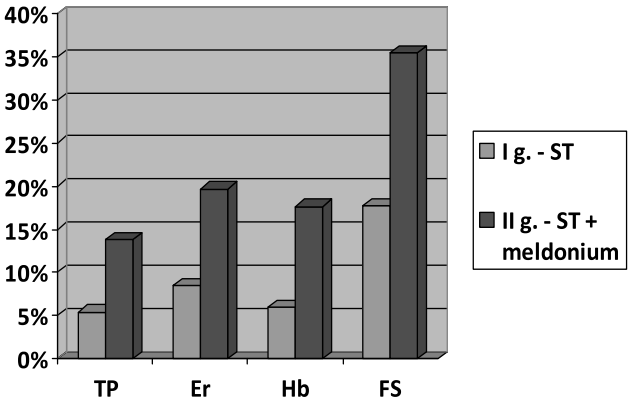

Image 2. *Percentage increase of indicators of trophological status in patients with comorbidity of CP and SCAD in two comparative groups*

Table 2

State of indicators of trophological status in patients with CP concomitant with SCAD before and after treatment in two comparative groups

Indicator	Control (n=20)	I group (n=45)		II group (n=45)	
		Before treatment	After treatment	Before treatment	After treatment
TP, g/l	74.58±1.96	62.84±0.77 *p<0.001	65.84±0.76 *p<0.001 **p<0.01	62.12±0.76 *p<0.001	70.02±0.85 *p<0.001 **p<0.01 ***p<0.05
Hb, g/l	135.95±1.67	101.17±1.87 *p<0.001	107.58±1.28 *p<0,001 **p<0,01	100.64±.055 *p<0.001	118.38±1.23 *p<0.001 **p<0.01 ***p<0.05
Er, × 10^{12}/l	4.36±0.08	3.23±0.09 *p<0.001	3.54±0,18 *p<0,001 **p<0,01	3.25±0.12 *p<0.001	3.89±0.36 *p<0.001 **p<0.01 ***p<0.05
TS, g/l	320.51±5.71	532.22±16.17 *p<0.001	485.87±28.93 *p<0.001 **p<0.01	527.99±19.72 *p<0.001	447.78±28.24 *p<0.001 **p<0.01 ***p<0.05
FS, mcmol/l	163.7±15.52	108.05±19.54 *p<0.001	131.31±33.00 *p<0.001 **p<0.01	102.81±16.25 *p<0.001	159.26±37.59 *p<0.001 **p<0.01 ***p<0.05

Notes:
* probability of difference regarding to such indicators of control;
** probability of difference regarding to such indicators of their patients with CP+SCAD before treatment;
*** probability of difference regarding to such indicators of patients in I group.

Conclusions

1) Using metabolic drug Vazonat (meldonium dihydrate) in treatment of patients with CP concomitant with SCAD contributed to more significant regression of prooxidant-antioxidant disturbances in comparison with standard conventional therapy.

2) Adding drug Vazonat (meldonium dihydrate) to the complex therapy of the patients with comorbid course of CP and SCAD contributed to higher improvement of indicators of trophological status according to the investigated parameters (p<0.05) in comparison with the standard basic therapy.

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