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Antoniv A.A.,
Tseberskyi K.A.
Bukovynian State Medical University

THE TREATMENT OF NON-ALCOHOLIC STEATOGEPATITIS IN COMORBID COURSE WITH CHRONIC KIDNEY DISEASE (CHRONIC PYELONEPHRITIS)

Антонів А.А.,
Цеберський К.А.
Буковинський державний медичний університет

ЛІКУВАННЯ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ ЗА КОМОРБІДНОГО ПЕРЕБІГУ З ХРОНІЧНОЮ ХВОРОБОЮ НИРОК (ХРОНІЧНИЙ ПІЄЛОНЕФРИТ)

Abstract.
The article presents a theoretical generalization of the results of the clinical efficacy of S-adenosylmethionine in patients with non-alcoholic steatohepatitis (NASH) in comorbidity with obesity and chronic kidney disease (CKD) of the 1st-2nd stages, which produces powerful membrane-stabilizing effects on the affected hepatocytes, which permanently eliminates clinical manifestations of the disease , the intensity of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, inhibits the progression of the hepatocellular and renal dysfunction (increases the albumin-synthesizing function of the liver and the glomerular filtration rate) by optimizing the control of liver and kidneys fibrosis.

Анотація.
У статті представлено теоретичне узагальнення результатів клінічної ефективності S-аденозилметіоніну у хворих на неалкогольний стеатогепатит (НАСГ) при супутніх захворюваннях з ожирінням і хронічною хворобою нирок (ХНП) 1-2 стадій, що продукує потужний мембрано-стабілізуючий вплив на уражені гепатоцити, що надовго усуває клінічні прояви захворювання, інтенсивність цитолізу, холестазу, мезенхімально-запального синдрому, гальмує прогресування гепатоцелюлярної та ниркової дисфункції (підвищує альбумін-синтезувальну та гломерну функцію печінки). швидкість фільтрації) шляхом оптимізації контролю фіброзу печінки та нирок.

Keywords*: non-alcoholic steatohepatitis, chronic kidney disease, S-adenosylmethionine.*
Ключові слова*: неалкогольний стеатогепатит, хронічна хвороба нирок, S-аденозилметіонін.*

Introduction. The comorbid flow of non-alcoholic steatohepatitis (NASH) and chronic kidney disease (CKD) has often recently attracted the attention of both practitioners and researchers [4, 9]. Without correction of clinical and biochemical syndromes of liver and kidney damage by interrupting the cascade of interactions, the cessation of the progression of their inflammation, the fibrosing of both organs and the restoration of their functional state can not be corrected [1, 7, 8, 9]. An important place in the pathogenesis of both diseases is the disturbance of carbohydrate and lipid homeostasis, oxidative and nitrosatitistic stress, endogenous intoxication that helps to accelerate apoptosis of hepatocytes, endothelium, and further their cytolysis on the background of autoimmunic cytokine mechanisms activation of inflammation progression and fibrosing reactions, which leads to progressive functional lack of organs [4, 9].

Therefore, among modern methods of treating patients with NASH and CKD, the use of correctors of several parts of the pathogenesis of most components with comorbidity with the probable normalization of the maximum number of parameters of homeostasis is important. [1, 4].

One of these drugs is S-adenosylmethionine (SAM), which, according to the literature, has detoxification, antioxidant, membrane-stabilizing properties (promoting the synthesis of glutathione), the ability to eliminate intrahepatic cholestasis (by activating enzymes that provide transport of bile micelles on the cholangiolar polypeptide of hepatocyte), and administrating antidepressant and regenerative effects [1, 2, 3, 5, 10].

At the same time, in Ukraine, the study of the effectiveness of SAM in patients with NASH on the background of obesity is isolated [1, 2, 3, 5], and on comorbidity with the CKD, in particular, with regard to the probable effect on the functional state of the kidneys - not conducted at all, which determines the relevance of conducting this research.

The object of the study. was to determine the likely effect of S-adenosylmethionine and Meldonium on the clinical course of non-alcoholic steatohepatitis (NASH) and chronic kidney disease (CKD) of the I-II stages.

Material and methods of research. We examined 75 patients with NASH with comorbid obesity I degree and CKD I and II dgrees. To determine the efficacy of the treatment, 3 groups of patients were randomized according to age, sex, degree of obesity, activity of the cytolytic syndrome of NASH and the stage of the CKD (chronic uncomplicated pyelonephritis with latent course in the phase of subsiding acute exacerbation). Control group (1) (24 persons) received a hypocaloric diet, metformin 500 mg twice daily, Essentiale H as a hepatoprotective drug (1 capsule 3 times a day), canephron (50 mg 3 times a day) for 90 days The

second group (2) (26 people) received a hypocaloric diet, metformin 500 mg twice daily, canephron (50 mg 3 times a day), adenosylmethionine (Ahepta) (SAM) as a hepatoprotective drug (200 mg 3 times on a sublingual day) for 90 days. The third group (3) (25 people) received a hypocaloric diet, metformin 500 mg twice daily, canephron (50 mg 3 times daily), SAM (200 mg 3 times daily sublingual), and Meldonium (vazonate) (V) (250 mg 2 times a day) as an energy, lipid, and carbohydrate metabolism stabilizer for 90 days. The average age of patients was (45.8 ± 3.81) years. During the study of cases of side effects of drugs has not been established.

The statistical analysis of the results was carried out in accordance with the type of research carried out and the types of numerical data that were obtained. Distribution normality was verified using Liliefors, Shapiro-Uilka tests and the direct visual evaluation of eigenvalues distribution histograms. Quantitative indices having a normal distribution are represented as mean (M) ± standard deviation (S). Discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of subjects surveyed). For comparisons of data that had a normal distribution pattern, parametric tests were used to estimate the Student's t-criterion, Fisher's F-criterion. In the case of abnormal distribution, the median test, Mann-Whitney Rank U-Score, and Wilcox's T-criterion (in the case of dependent groups) were used for multiple comparison. Statistica for Windows version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages were used for statistical and graphical analysis of the obtained results.

Results of the study and their discussion. The analysis of the effects of SAM and SAM with (V) in course of therapy of patients with NASH and CKD (group 2 and 3) on the course of the disease compared to the control group (group 1) showed the following results (Table 1). Improvement of well-being, reduction of signs of astheno-vegetative, intoxication syndrome and dyspeptic manifestations in patients of groups 2nd and 3rd were observed 3-4 days after treatment, whereas in patients with 1st group only 10 days. 4 weeks after the start of therapy, the manifestation of astheno-vegetative syndrome in patients 2nd and 3rd groups was significantly less than in 1st group: respectively, in 1,3 and 1,8 times (p <0,05). After a month of treatment, patients in groups 2 and 3 marked a significant increase in physical and mental working capacity, which exceeded the rate in patients in group 1, respectively, in 1.6 and 1.9 times (p <0.05).

The existing manifestations of depression in patients 2nd and 3rd groups significantly decreased and in most patients disappeared, which exceeded the effectiveness of the influence of traditional therapy in patients 1st group - respectively, in 3,6 and 4,3 times (p <0,05) (Table 1). The comparative dynamics of the intensity of the main clinical syndromes on the 30th day of treatment was as follows: the general manifestations of the dyspeptic syndrome decreased in comparison with the indicator after treatment in patients 1st group, respectively, in 2nd group - in 2,4-2,9 times (p <0, 05), in 3rd group - in 2,8 - 3,2 times, clinical manifestations of cholestasis - respectively, in 2,9 and 3,1 times (p <0,05), of the basic discomfort (severity, pain) - 1,8 and 2.0 times (p <0,05), hepatomegaly - 1,3 and 1,5 times respectively (p <0,05).

Indicators of biochemical markers of the functional state of the liver and kidneys in the dynamics of treatment are illustrated in Table. 2. Within 30 days of the initiation of treatment, a probable decrease in the total bilirubin content in the blood was recorded only in patients with 2nd and 3rd groups: 1.4 and 1.8 times respectively (p <0.05) with the achievement of standard limits (p> 0 , 05), while in patients in 1st group there was only a tendency to decrease (p> 0,05). After 90 days of treatment, the reduction was more significant: 1.8 and 2.1 times respectively (p <0.05) with unlikely changes in 1st t group. Only after 3 months. After treatment in 1st group, the total bilirubin content decreased significantly, however, the normative indicators did not reach (p> 0.05), whereas in the 2nd and 3rd groups the indicators remained within the normative (p> 0.05) throughout the entire observation period.

The content of conjugated bilirubin at 30 days of treatment in patients 2nd and 3rd group was decreased by 1.8 and 2.0 times with normalization (p <0.05), while changes in 1st group were unlikely (p> 0.05), which indicates the powerful membrane-protective properties of the sublingual form of SAM and its ability to eliminate the hepatocyte cytolysis syndrome and the cholestatic component of NASH (Table 2). At the same time, the combination and SAM and V had a more effective effect on pigment exchange correction, as evidenced by the likely difference between the indicator 30 days after treatment in patients 2nd and 3rd groups (p <0.05). A similar trend towards the content of total bilirubin was observed in relation to its direct fraction after 90 days of treatment, as well as in 3 months after treatment with stable normalization of indicators only in patients in 2nd and 3rd groups (p> 0.05).

Integrated therapy involving SAM and SAM with V has also significantly accelerated the conjugation processes of the free fraction of bilirubin with a decrease in its content in the blood for 30 days of treatment - respectively, in 1,3 and 1,6 times (p <0,05), at 90 Day of treatment - in 1,6 and 1,9 times (p <0,05) and continued to decrease for 3 months after treatment (p <0,05), in contrast to traditional therapy, where the reduction of unconjugated bilirubin in the month of treatment was 1,2 times, after 3 months of treatment - the rate decreased by 1,3 times, however, the normative values were not reached (p <0,05). In patients of 2nd and 3rd groups, the normalization of pigmentary metabolism rates was stable and stable both before the end of the course of treatment and in the long term (3 months).

Another confirmation of the possibility of eliminating the manifestation of the cytolytic syndrome in patients with NASH during one month of treatment is a possible decrease in the activity of AST in the blood: 11.2%, 48.4% and 60.0% respectively (p <0.05), moreover, with a significantly higher efficiency of complex therapy with SAM with V (p <0,05). After 90 days of follow-up, the decrease in the activity of AST was more significant than in the first observation period: 1.6

times, 3.1 and 4.2 times (p <0.05), with stable normalization of the indicator only in patients 2nd and 3rd groups (p> 0.05). We also found a decrease in the activity of ALT on the 30th day of treatment in patients 2nd and 3rd groups: respectively, 2.3 and 2.8 times (p <0.05), compared with only the tendency to decrease (p> 0.05) in group 1 , with a probable intergroup difference (p <0,05). It should be noted that the activity of AST and ALT in patients with NASH 1 group in the treatment dynamics remained significantly elevated during the entire observation period, which required the appointment of an additional course of treatment. The use of SAM and SAM with V also produced a powerful anti-inflammatory effect. Thus, in patients with 2nd and 3rd groups in the dynamics of treatment, the thyme test decreased by 1.2 and 1.3 times (p <0.05) with unlikely changes in group 1 (p> 0.05); The albumin / globulin ratio increased by 1.3 and 1.4 times (p <0.05) versus the growth trend in group 1 (p> 0.05). The highest anti-inflammatory effect of SAM therapy with V versus the appointment of SAM alone is evidenced by the results of the study of the thyme sample after 90 days of treatment: a decrease of 1.3 and 1.5 times (p <0.05) and 3 months later after treatment with a stable normalization of the indicator (p> 0.05).

In the dynamics of treatment with SAM and SAM with V, a significant increase in the liver protein function was found (albumin content in the 2nd and 3rd groups increased 1.3 times (p <0.05) versus 7.7% (p> 0.05) in group 1) and a probable increase in the content of total protein in the blood, respectively, in 1,3 and 1,4 times (p <0,05) versus 1,2 times in group 1, 3 months after treatment (p <0,05). Thus, SAM possesses powerful membrane-stabilizing properties, stably eliminates the manifestations of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, increases the albumin-synthesizing function of the liver in patients with NASH and prevents the loss of albumins in the conditions of CKD I-II st. At the same time, complex therapy SAM with V is superior to the effectiveness of correction of these syndromes due to the implementation of powerful metabolic, antioxidant, antihypoxant, energy-specific properties of Meldonium [6, 7, 8] and may be recommended for the introduction into the practice of internal medicine and gastroenterology for treatment NASH on the background of obesity and CKD I and II stages.

Analyzing the functional status of the kidneys in the examined patients in the dynamics of treatment, it should be noted that the proposed therapy of SAM and SAM with V contributed to the correction of a significantly reduced GFR (Table 2) after 30 days treatment with an increase of 1.2 and 1.4 times, respectively (p <0.05). In the distant term, a stable normalization of the indicators in patients with 2nd and 3rd groups was observed, with an increase of 1.3 and 1.5 times, respectively (p <0.05). The established nephroprotective properties of SAM that are potentially Meldonium are probably due to the ability of these drugs to eliminate endothelial dysfunction, improve microcirculation, and prevent the progression of kidney fibrosis [6, 7, 8].

Conclusion. S-adenosylmethionine (ahepta) in a dose of 600 mg sublingually in patients with non-alcoholic steatohepatitis on the background of obesity and chronic kidney disease of the 1st and 2nd st. produces powerful membrane-stabilizing effects on the affected hepatocytes, stably eliminates the clinical manifestations of the disease, the intensity of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, inhibits the progression of hepatic and renal dysfunction (increases the albumin-synthesizing function of the liver, the velocity of glomerular filtration) by optimizing the control of fibrosis of the liver and kidneys. Complex therapy with S-adenosylmethionine (ahape) and Meldonium (500 mg / day vasonate) is superior to the correction of these syndromes NASH and CKD, since the vasonate potentially potentiates the action of S-adenosylmethionine in acute and distant observation periods.

Promising further research in this area. is the establishment of probable mechanisms of the influence of S-adenosylmethionine and Meldonium on the course of chronic kidney disease and non-alcoholic steatohepatitis on the background of obesity, the intensity of oxidative and nitrosatitistic stress, functional state of the endothelium and the intensity of fibrous reactions in the liver and kidneys.

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Table 1.

Intensity of clinical symptoms of non-alcoholic steatohepatitis (in points) in patients with obesity and CKd I-II st. in the dynamics of treatment.

Clinical symptom	The group surveyed patients		
	Group 1, n=24	Group 2, n=26	Group 3, n=25
General weakness (asthenia)	2,6±0,17	3,5±0,19 *	4,7±0,12*/**
Capacity (physical, mental)	2,4±0,11	3,9±0,12 *	4,6±0,15*/**
Depression	1,1±0,13	4,0±0,08 *	4,7±0,09 */**
Bitterness in the mouth	1,5±0,22	4,3±0,08 *	4,8±0,12*/**
Dryness in the mouth	1,7±0,12	4,1±0,16 *	4,7±0,15*/**
Nausea	1,5±0,17	4,0±0,05 *	4,6±0,10*/**
Bloating	1,9±0,12	4,5±0,15 *	4,6±0,17 *
Itchy skin	1,6±0,08	4,6±0,07	4,9±0,02*/**
Heaviness in the right subcostal area	2,4±0,12	4,4±0,11*	4,9±0,09*/**
Hepatomegaly	3,2±0,13	4,1±0,10 *	4,7±0,09*/**
Notes: 1. Scale of assessment: 1 point - negative effect; 2 points - no effect; 3 points-satisfactory; 4 points - good; 5 points - very good. 2. * - differences are probable compared to the group of patients treated with Essentsial H (p <0,05); ** - the differences are likely compared with the group of patients treated with adenosylmethionine (p <0.05);			

Table 2.

Biochemical parameters of the functional state of the liver and kidneys in patients with non-alcoholic steatohepatitis and chronic kidney disease I-II st. in the dynamics of treatment (M ± m)

Indicator	Practically healthy person, n=20	Group	Before treatment	After 30 days	After 90 days	After 3 months of treatment
Total bilirubin, μmol / l	19,2±1,12	1	35,2±1,03 *	30,9±4,1*	28,9±3,8 *	25,2±3,7 */**
		2	35,6±1,08 *	24,8±1,01 **/#	20,2±0,76 **/#	19,1±0,73 **/#
		3	35,3±1,16 *	20,2±1,05 **/#/***	16,9±0,83 **/#/***	16,2±0,48 **/#/***
Direct bilirubin, μmol / l	4,5±0,25	1	10,2±0,35 *	9,5±0,97*	8,9±1,10 *	7,4±0,73 */**
		2	10,1±0,37 *	5,7±0,21 **/#	4,7±0,05 **/#	4,6±0,05 **/#
		3	10,1±0,31 *	5,0±0,13 **/#/***	4,4±0,03 **/#/***	4,4±0,04 **/#/***
Indirect bilirubin, μmol / l	14,7±0,43	1	25,0±1,13 *	21,4±0,27 */**	20,0±0,45 */**	17,8±1,23 **
		2	25,5±1,08 *	19,1±0,35 */**/#	15,5±0,35 **/#	14,5±0,64 **/#
		3	25,1±1,16 *	15,2±0,21 **/#/***	13,5±0,37 **/#/***	11,8±0,52 */**/#/***
AST, μmol / hour×l	0,39±0,01	1	1,25±0,02*	1,11±0,02 */**	0,8±0,02 */**	0,6±0,03 */**
		2	1,24±0,01 *	0,6±0,01 */**/#	0,4±0,01 **/#	0,4±0,03 **/#
		3	1,25±0,01 *	0,5±0,01 */**/#/***	0,3±0,01 **/#/***	0,4±0,02 **/#
ALT, μmol / hour×l	0,38±0,014	1	1,4±0,02 *	1,2±0,08 *	0,8±0,03 */**	0,7±0,05 */**
		2	1,4±0,02 *	0,6±0,02 */**/#	0,5±0,02 */**/#	0,4±0,02 **/#
		3	1,4±0,01 *	0,5±0,02 */**/#/***	0,4±0,01 **/#/***	0,4±0,01 **/#
Total protein, g/l	76,13±2,12	1	60,30±2,11*	65,26± 2,25*	66,5±2,39 *	70,3±2,53 **
		2	60,31±1,92*	75,8±2,31**	78,2±2,04 **/#	81,2±2,31 **/#
		3	60,28±1,84*	80,2±2,37 **/#	82,3±2,13 **/#	82,6±2,12 **/#

Albumin, %	59,37±2,23	1	43,63±2,33*	45,32± 1,97*	50,42± 1,79*	51,0± 1,92*
		2	43,62±2,34 *	54,83± 1,35**/#	59,27±1,25 **/#	59,8±1,18 **/#
		3	43,63±2,35 *	57,15± 1,42**/#	60,42±1,34 **/#	60,1±1,24 **/#
Bile acid, mmol/l	1,27± 0,01	1	2,83±0,06 *	2,74± 0,35*	2,72± 0,53*	2,60± 0,17*
		2	2,81±0,08 *	2,12±0,03 */**/#	1,57±0,05 **/#	1,39±0,04 **/#
		3	2,82±0,07 *	1,94±0,05 */**/#/***	1,36±0,02 **/#/***	1,20±0,05 **/#/***
Thymol test, conditional units	2,82± 0,13	1	4,30±0,15*	4,24±0,21*	4,13±0,13*	4,01±0,21*
		2	4,33±0,13*	3,53±0,17 */**/#	3,21±0,07 */**/#	3,09±0,08 **/#
		3	4,32±0,12*	3,41±0,10 */**/#	2,90±0,06 */**/#/***	2,76±0,07 **/#/***
Glomerular filtration rate, ml/min	117,0±3,37	1	78,5± 3,26*	80,2± 3,75*	82,7±3,14*	87,3±3,79*
		2	78,3± 3,25*	96,5±2,43 */**/#	100,2±2,64 **/#	105,8±2,28 **/#
		3	78,6± 3,28*	106,8±2,27 */**/#/***	112,5±2,51 **/#/***	116,1±2,39 **/#/***

Notes: 1. * the difference is probable compared to the indicator for practically healthy persons ($p < 0,05$); 2. ** the difference is probable compared with the indicator before treatment ($p < 0,05$); 3. # - the difference is probable compared to the indicator after treatment in patients in group 1 ($p < 0.05$); 4. *** - the difference is probable compared to the indicator after treatment in patients in group 2 ($p < 0,05$).