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EFFICACY OF BICYCLOL APPLICATION IN COMPLEX TREATMENT OF NON-ALCOHOLIC STEATHOHEPATITIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Key words: *non-alcoholic steatohepatitis, type 2 diabetes mellitus, treatment, bicyclol.*

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The aim of research *– to establish the probable effect of Bicyclol on the clinical manifestations of nonalcoholic steatohepatitis, markers of hepatocyte cytolysis, cholestasis, mesenchymal inflammation in patients with nonalcoholic steatohepatitis nonalcoholic steatohepatitis, and diabetes mellitus of type 2, the degree of hepatocyte steatosis and the stage of liver fibrosis.*

Methods. *Studies were conducted in the treatment dynamics of 60 patients with NASH with diabetes mellitus of type 2 of moderate severity. Clinical, biochemical, sonographic, bibliosemantic, statistical methods were used.*

Results. *The effectiveness of Bicyclol exceeded the intensity of therapeutic effect of traditional therapy (essential phospholipids) by reducing the intensity of clinical syndromes of anonalcoholic steatohepatitis: astheno-vegetative, abdominal discomfort, dyspepsia, cholestasis, hepatomegaly ($p<0,05$), as well as the activity of biochemical syndromes: cytolysis, cholestasis, mesenchymal inflammation ($p<0,05$), decreased steatosis ($p<0,05$), and contributed to the reversal of liver fibrosis ($p<0,05$).*

Conclusions. *Bicyclol treatment is more effective than traditional nonalcoholic steatohepatitis therapy against a background of diabetes mellitus of type 2 and may be recommended for use as first-line therapy for 3 months 1 or 2 times a year.*

Ключові слова: *неалкогольний стеатогепатит, цукровий діабет типу 2, лікування, біциклол.*

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ЕФЕКТИВНІСТЬ ЗАСТОСУВАННЯ БІЦИКЛОЛУ У КОМПЛЕКСНОМУ ЛІКУВАННІ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ ТИПУ 2

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Мета дослідження *– встановити ймовірний вплив біциклолу на клінічні прояви неалкогольного стеатогепатиту, маркери цитолізу гепатоцитів, холестазу, мезенхімально-запального синдрому у хворих на неалкогольний стеатогепатит та цукровий діабет 2-го типу, ступінь стеатозу гепатоцитів і стадію фіброзу печінки.*

Матеріал та методи. *Проведено дослідження динаміки лікування 60 хворих на неалкогольний стеатогепатит (НАСГ) із цукровим діабетом 2-го типу середнього ступеня тяжкості з використанням клінічного, біохімічного, сонографічного, бібліосемантичного, статистичного методів.*

Результати. *Встановлено, що ефективність біциклолу перевищувала інтенсивність терапевтичного ефекту традиційної терапії (есенціальні фосфоліпіди) за рахунок зниження інтенсивності клінічних синдромів НАСГ: астено-вегетативного, абдомінального дискомфорту, диспепсії, холестазу, а також гепатомегалії ($p<0,05$), активності біохімічних синдромів: цитолізу, холестазу, мезенхімального запалення ($p<0,05$), зменшення стеатозу ($p<0,05$), та сприяло усуненню фіброзу печінки ($p<0,05$).*

Висновки. *Лікування біциклолом неалкогольного стеатогепатиту на тлі цукрового діабету 2 ефективніше, ніж традиційна терапія, і може бути рекомендоване для застосування в якості терапії першої лінії протягом 3 місяців 1 або 2 рази на рік.*

Introduction

An urgent problem today is the early diagnosis and treatment of non-alcoholic fatty liver disease (NAFLD), in particular, such a clinical form as non-alcoholic steatohepatitis (NASH) in patients with type 2 diabetes mellitus (DM2) [1, 2]. In most cases, the disease is benign and the therapy recommended by standard patient management protocols [3], in particular, the use of vitamin E (in patients with NASH without DM2), omega-3 fatty acids, essential phospholipids, L-carnitine, lecithin, choline, B vitamins: B1, B6, B12, folic acid, metformin and pioglitazone eliminates cytolysis, suppresses inflammation and restores metabolic processes in hepatocytes. However, under certain conditions, against a background of decompensation of carbohydrate metabolism, the presence of complications of diabetes mellitus2 (micro-, macroangiopathy, neuropathy, nephropathy) – NASH may progress to

resistant in treatment cytolytic and mesenchymal-inflammatory syndromes [4]. In such cases, program therapy is ineffective and needs to be optimized [4].

Given information on the effectiveness of the drug Bicyclol, which has a number of properties, including anti-inflammatory, antioxidant, antifibrotic, and effective in viral hepatitis and liver cirrhosis [1,5,6,7-20], the working hypothesis of our work was to study the probable effectiveness of Bicyclol in NASH against a background of DM2. Bicyclol has been shown to be a complex synthetic drug [1,5-7], which is able to eliminate cytolysis of hepatocytes of different genesis [8-20] by inhibiting the production of free radicals and proinflammatory cytokines by neutrophils, Kupffer cells and macrophages, inhibition of ferroptosis, etc. [6]. At the same time, current data on the effectiveness of Bicyclol in patients with NASH against a background of DM2 in the literature are few, which led to the feasibility of our study.

The aim of the study

To determine the probable effect of bicyclol on the clinical manifestations of NASH, markers of hepatocyte cytolysis, cholestasis, mesenchymal inflammation in patients with NASH and DM2, the degree of hepatocyte steatosis and stage of liver fibrosis.

Material and methods

Studies in the treatment dynamics of 60 patients with NASH with DM2 of moderate severity, of which 15 people (25.0%) had DM2 in the compensatory stage, 45 (75.0%) subcompensated. In addition to DM2 in patients with NASH at the time of inclusion to the study was not found other chronic somatic pathology in the active phase or in the stage of decompensation (heart, blood vessels, kidneys, digestive system, blood and hematopoiesis, neurological, psychiatric, cancer, endocrine, rheumatic diseases, fatty liver disease of alcoholic etiology), acute illness, pregnancy, lactation

Depending on the prescribed treatment on a random basis, the examined patients were divided into 2 groups: (1 group – control: 28 people) received a low-calorie diet with dietary restrictions № 9, essential phospholipids (EPL) (Essentiale forte H (Sanofi-Avensis / Natter, Germany) 300 mg 2 capsules 3 times a day 90 days for the treatment of active NASH, for DM2 and hyperlipidemia metformin hydrochloride (Metformin-Teva, Teva Operations, Poland) 1000 mg per day for 90 days was prescribed. Group 2 (main) consisted of patients (32 people) who, in addition to similar dietary recommendations, metformin, instead of EPL received Bicyclol (Beijing Union Pharmaceutical Factory, China) 25 mg 3 times a day for 90 days. The mean age of patients was (53.8 ± 3.52) years. The comparison group consisted of 30 healthy individuals (HI) of the appropriate age.

NASH was diagnosed in accordance with the unified clinical protocol approved by the order of the Ministry of Health of Ukraine № 826 of 06.11.2014 [6], in the presence of criteria for excluding chronic diffuse liver disease of viral, hereditary, autoimmune or drug origin, as the cause of cytolytic, mesenchymal-mesenchymal-inflammatory with biochemical FibroMax Test, which included «SteatoTest», «ASH» and «NASH-Test» (BioPredictive, France) – to determine the degree of steatosis of the liver and its nature (alcoholic or non-alcoholic), «FibroTest» – to determine the stage of fibrosis liver, as well as on the basis of the results of ultrasonography (USG) on the on ultrasonographic (US) scanner Ultima PA («Radmir», Kharkiv, Ukraine).

Diagnosis of type 2 diabetes was carried out in accordance with the unified clinical protocol approved by the Order of the Ministry of Health of Ukraine № 1118 of 21.12.2012.

The dynamics of treatment assessed the clinical symptoms of diseases (astheno-vegetative, abdominal discomfort, dyspepsia, hepatomegaly, cholestasis), ultrasonographic (USG) picture of the liver, markers of damage (cytolytic syndrome: blood bilirubin, alanine aminotransferase (ALT) activity, aspartate aminotransferase (AST), cholestatic syndrome (direct bilirubin in the blood, alkaline phosphatase (AP), gamma-glutamine transferase (GGT), mesenchymal-inflammatory syndrome (thymol test), results of «SteatoTest» and «FibroTest», before treatment and on day 90 of treatment.

The research was carried out in compliance with the basic provisions of the GSR (1996), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Helsinki Declaration of the World Medical Association on ethical principles of scientific medical research with human participation (1964-2013), order of the Ministry of Health of Ukraine № 690 of 23.09.2009, № 616 of 03.08.2012

Before testing the statistical hypotheses, the normality of the distribution of values in randomized samples was analyzed by determining the asymmetry and excess coefficients using the Khan-Shapiro-Wilkie test. The probability of the difference between the arithmetic mean and its error between the study groups was determined using the two-sided odd Student's t-test. The difference was considered significant at a significance level of $p < 0.05$. Student's t-test was used only in the case of a normal distribution of the equality of the general variances of the compared samples, which was checked using Fisher's F-test. In other cases, the nonparametric Mann-Whitney rank test was used to compare the results. The probability of changes in the dynamics of treatment in the case of normal distribution in the samples was determined by the Student's paired test, in other cases – by the non-parametric paired Wilcoxon paired T-test. Statistica for Windows versions 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA) were used for statistical analysis of the obtained results.

Research results and their discussion

In the dynamics of treatment with Bicyclol group 2 there was a more intense reduction in clinical manifestations of the disease and normalization of patients' well-being (Table 1). In particular, after treatment, symptoms of astheno-vegetative syndrome (AVS) in group 1 were observed 1.6 times less often ($p>0,05$) than the proportion of patients in whom manifestations were recorded before treatment, while in group 2 manifestations of AVS in frequency their

manifestations were registered in 8.3 times fewer people who had this syndrome before treatment (p<0,01) with a significant difference in the frequency of ABC between groups after treatment (p<0,05). Pain / discomfort / heaviness in the right hypochondrium was disturbing after treatment in groups 1 and 2, respectively – in 1,7 and 12,3 times less share of patients compared to the proportion of patients in whom manifestations were recorded before the treatment (p<0,01), with a significant difference in the frequency of manifestation of this syndrome in the intergroup aspect (p<0,01). On the 90th day of treatment, positive dynamics was observed for cholestasis syndrome only in 2 groups of patients, which at the end of treatment was present only in 3 (9,4%) people (p<0,05), which was a decrease in the incidence of the syndrome in 4,4 times (p <0,01), at the same time, changes in the control group were unlikely (p>0,01).

In patients of both groups of comparison after treatment significantly reduced the manifestations of dyspepsia: disappeared nausea, belching air, bloating disappeared. Thus, after treatment, the symptoms of dyspepsia in group 1 were observed 1,3 times less often (p>0,05) than the number of patients in whom these manifestations were recorded before treatment, while in group 2 manifestations of dyspeptic syndrome by frequency of their manifestations were registered 4,6 times fewer people than those who had this syndrome before treatment (p<0,01) with a significant difference between the groups after treatment (p<0,05). Symptoms of hepatomegaly after treatment were observed much less frequently in both groups: in group 1-1,6 times less often, and in group 2-4,0 times (p<0,01) with a significant difference in the frequency of this syndrome between groups (p<0,05).

Table 1

Dynamics of clinical symptoms and syndromes in patients with NASH and DM2 before and after treatment (n,%)

Symptoms and syndromes	Group	Before treatment, n (%)	On the 90th day of treatment, n (%)	p0-90	P – between groups BT – before treatment AT – after treatment
Astheno-vegetative	1	14 (50,0%)	10 (31,3%)	>0,05	p1-2BT=0,56 p1-2AT=0,02
	2	16 (50,0%)	2 (6,3%)*/**	<0,01*	
Discomfort/ pain in the right hypochondrium	1	10 (35,7%)	6 (21,4%)	>0,05	p1-2 BT =0,42 p1-2 AT =0,03
	2	12 (37,5%)	1 (3,1%) */**	<0,01*	
Dyspepsia	1	13 (46,4%)	10 (35,7%)	>0,05	p1-2 BT =0,22 p1-2 AT =0,21
	2	15 (46,9%)	3 (10%)*/**	<0,01*	
Hepatomegaly	1	28 (100%)	18 (64,3%)	<0,01*	p1-2 BT =0,12 p1-2 AT =0,03
	2	32 (100%)	8 (25,0%)*/**	<0,01*	
Cholestasis syndrome	1	11 (39,3%)	9 (32,1%)	>0,05	p1-2 BT =0,16
	2	13 (40,6%)	3 (9,4%)*/**	<0,01*	p1-2 AT =0,04

Positive changes due to the prescribed therapy were observed during a repeated USG study (on the 90th day of therapy): the echostructure of the liver parenchyma was restored, the size of the liver and spleen decreased (Table 2). In particular, the vertical size of the right lobe of the liver on the 90th day of treatment decreased 9,6% (p<0,05) in group 1, 19,3% (p<0,05) in group 2, the vertical size of the left lobe liver – 1,3 times (p<0,05) in group 1, and 1,5 times (p<0,05) in group 2 with a significant difference between 1 and 2 groups (p <0,05).

Table 2

Dynamics of ultrasonographic parameters of the liver in patients with NASH and DM2 at the end of treatment, (M±m)

Indicator	HI	Group	Before treatment	On the 30th day of treatment
Vertical size of the right lobe of the liver, mm	131,3±4,2	1	181,8±5,6*	163,7±2,5*/**
		2	180,1±5,2*	145,2±3,1**/#
Vertical size of the left lobe of the liver, mm	61,5±1,8	1	95,7±2,5*	72,3±2,0*/**
		2	95,1±2,3*	65,7±1,2**/#

Notes:

** – the difference is significant compared to healthy individuals (p<0,05);*

*** – the difference is significant compared to the indicator before treatment (p<0,05);*

 # – the difference is significant compared to group 1 (p<0,05). Analysis of biochemical parameters in patients with NASH in the dynamics of treatment showed a probable decrease in total bilirubin in the blood of patients 1 and 2 groups: 1,4 (p<0,05) and 2.3 times (p<0,05) in accordance with a more significant decrease until the normalization of this indicator in group 2 (p<0,05) (Table 3). The content of direct bilirubin in the blood of patients with NASH was significantly reduced in patients of both groups: in group 1-1,6 times (p<0.05), in group 2-2,6 times (p<0,05), with probable difference between the 1st and 2nd groups (p<0,05); the level of conjugated bilirubin in patients of group 2 reached the normative values and did not differ significantly from that in HI (p>0,05). Regarding the content of indirect bilirubin, the dynamics was as follows: on the 90th day of treatment, its content in the blood decreased significantly in patients of groups 1 and 2 – respectively 1,3 (p<0,05) and 2,1 times (p<0,05).

Table 3

Indicators of liver damage and functional status in patients with non-alcoholic steatohepatitis and DM2 in the dynamics of treatment, (M ± m)

Indicator	HI (n = 30)	Group	Before treatment	On the 90th day of treatment
Total bilirubin, μmol / l	15,48±0,62	1	37,25±1,14*	26,87±1,10*/**
		2	36,37±1,21*	16,26±0,54 **/#
Direct bilirubin, μmol / l	5,81±0,31	1	13,11±0,74*	8,39±0,46*/**
		2	13,28±0,81*	5,22±0,23**/#
Bilirubin indirect μmol / l	9,67±0,25	1	24,14±0,93*	18,48±0,87*/**
		2	23,09±0,98*	11,04±0,53**/#
ALT, un/l	21,30±1,01	1	89,33±2,72*	38,27±2,15*/**
		2	90,15±2,85*	20,54±1,67**/#
AST, un/l thymol test	21,67±1,13	1	67,31±1,49*	35,37±1,61*/**
		2	68,18±1,51*	19,26±1,08 **/#
GGT, un/l	24,45±1,15	1	59,42±2,56*	46,63±2,47*/**
		2	60,28±2,52*	26,86±1,73**/#
AP, un/l	74,62±5,34	1	158,82±7,47*	117,53±6,95*/**
		2	159,24±7,51*	78,35±5,17**/#
Thymol test, unit	2,30± 0,06	1	4,78±0,20 *	4,13±0,14*
		2	4,77±0,24*	2,55±0,08 **/#

Notes:

** – the difference is significant compared to healthy individuals (p<0,05);*

*** – the difference is significant compared to the indicator before treatment (p<0,05);*

 # – the difference is significant compared to group 1 (p<0,05).At the same time, patients of group 2 showed complete normalization of the indicator on day 90. Regarding the correction of the parameters of the cytolytic syndrome, after treatment there was a decrease in ALT activity in patients of all groups: in group 1-2,3 times (p<0,05), in group 2-4,5 times, respectively (p<0,05) with a probable intergroup difference (p<0,05) with complete normalization of this indicator in patients of group 2 (p>0,05). Similar dynamics was observed in the groups of patients with a decrease in AST activity: the decrease in the 1st group was 1,9 times (p<0,05), the 2nd – 3,6 times (p<0,05), according to the probable intergroup the difference (p<0,05). This dynamics of changes in aminotransferases suggests that in patients with NASH and DM2 the maximum impact on the elimination of cytolytic syndrome had the appointment of Bicyclol. The positive effect of Bicyclol on the elimination of the syndrome of intrahepatic cholestasis is evidenced by a decrease in the activity of GGT and AP. Thus, in patients of group 2 there was a probable decrease in GGT activity (2,3 times (p<0,05) with its normalization in patients of group 2 against a decrease of 1,3 (p<0,05) times in group 1. At the same time, the activity of AP after treatment was significantly reduced in group 1 by 1,4 times (p<0,05), in group 2 – by 2,0 times (p<0,05) with a probable intergroup difference (p< 0,05). The higher anti-inflammatory effect of Bicyclol therapy against the appointment of EPL is evidenced by the results of a study of thymol test, which after treatment decreased significantly only in patients of group 2-1,8 times (p<0,05) versus 1,2 times (p>0,05) in the 1st group.

Increased pre-treatment hepatocyte steatosis, which exceeded the reference values by 4,0 times (p <0.05) – under the influence of treatment also probably decreased in patients 1 and 2 observation groups – 1,2 and 1,8 times (p (<0,05) with the presence of a probable intergroup difference (p<0,05) (Table 4).

Table 4

Indicators of the degree of hepatocyte steatosis (according to steato-test) and the index of liver fibrosis (according to fibro-test) in patients with non-alcoholic steatohepatitis, type 2 diabetes mellitus in the dynamics of treatment (M±m)

HI	Indicators	Groups of examined patients	
		Group 1 (n=28)	Group 2 (n=32)
	Steato test	0,19±0,02	
	Fibro test	0,17±0,01	
Before treatment	Steato test	0,75±0,02 *	0,76±0,02 *
	Fibro test	0,56±0,01 *	0,55±0,01 *
On the 90th day of treatment	Steato test	0,61±0,02 */**	0,42±0,01 */**/#
	Fibro test	0,50±0,01 */**	0,33±0,01 */**/#

Note:

** – the difference is probable in comparison with the indicator in HI (p <0,05);*

*** – the difference is probable in comparison with the indicator before treatment (p <0,05);*

 # – the difference is probable in comparison with the indicator after treatment in patients of group 1 (p <0,05). Thus, both traditional treatment with essential phospholipids and the drug Bicyclol have an active effect and during 90 days of treatment reduce the main components of the pathological process in the liver in NASH – cytolysis and fatty degeneration of hepatocytes, but Bicyclol in complex hypoglycemic and hypoglycemic and hypotensive. At the same time, the effect of traditional therapy on the activity of liver fibrosis, according to the results of our studies, was probably lower than the proposed therapy with Bicyclol. In particular, the increased pre-treatment rate of FibroTest (3,2 times, p<0,05) in the dynamics of treatment in patients of group 1 decreased 10,7% (p<0,05), and in patients of group 2-40,0% (p<0,05) with the presence of a probable intergroup difference (p<0,05). The data obtained indicate a favorable anti-inflammatory effect of Bicyclol, which helps to inhibit liver fibrosis.

Thus, the appointment of Bicyclol in NASH against a background of diabetes is effective, as a positive effect of the drug on the leading clinical and biochemical syndromes of NASH, which is slightly higher than the intensity of traditional therapy with essential phospholipids. The explanation of this process is the basis of the pharmacological properties of the drug. Bicyclol has been shown to inhibit oxidative stress, restore the structure of the nucleus and deoxyribonucleic acid (DNA), the functional state of hepatocyte mitochondria, prevent apoptosis and counteract hepatocyte necrosis, help to restore the functional state of hepatocytes, inhibits the processes of fibrosis of liver tissue [1,5, 8-20]. A number of studies have been conducted to prove the effectiveness of Bicyclol in alcoholic fatty liver disease [1,5-7], toxic and drug-induced hepatitis [8-17,19,20], for liver rehabilitation after chemotherapy and chemoprophylaxis of posttransplant reactions in kidney transplantation [18] etc.

Conclusions

1. Treatment with Bicyclol for 3 months of non-alcoholic steatohepatitis in patients with DM2 is effective in significantly reducing the intensity of manifestations astheno-vegetative, dyspeptic, cholestatic syndromes, abdominal discomfort and hepatomegaly.

2. The use of Bicyclol for 3 months helped to eliminate the biochemical syndromes of NASH in patients with DM2: cytolysis, cholestasis, mesenchymal inflammation ($p<0,05$) with complete normalization of their markers, promotes the probable reversal of hepatocyte steatosis and decreased hepatic fibrosis.

3. The course of treatment is recommended for patients with NASH against a background of DM2 for 90 days once or twice a year.

The prospect of further research

will be the study of clinical and biochemical manifestations of NASH, blood glucose levels, degree of insulin resistance, blood lipid spectrum in patients with type 2 diabetes with diabetic nephropathy in the dynamics of treatment with Bicyclol.

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