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Intensity of systemic proteolysis and endotoxemia in patients with non-alcoholic steatohepatitis associated with obesity and comorbid chronic obstructive pulmonary disease in the dynamics of treatment with hepatoprotectors

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Abstract. Background. The prevalence of non-alcoholic steatohepatitis (NASH) and chronic obstructive pulmonary disease (COPD) is gaining global significance in the population of economically developed countries with a growing trend in Ukraine. The purpose was the determination of the intensity of systemic proteolysis and endogenous intoxication before treatment and the efficacy of hepatoprotective therapy in patients with NASH against the background of obesity, depending on the comorbidity of COPD. **Materials and methods.** Seventy-six patients with NASH, grade 1 obesity and COPD 2–3 D were screened and divided into 3 groups according to the treatment received. The control group (C group) consisted of 23 patients receiving basic treatment for NASH (essential fatty acids complex 300 mg 2 capsules 3 times daily) for 30 days and baseline COPD therapy. Twenty-five patients (group 2 — primary, O1), in addition to similar COPD therapy, for the treatment of NASH, instead of essential fatty acids complex, received antral at a dose of 200 mg 3 times a day for 30 days. The third group (basic, O2) involving 28 patients with NASH, grade 1 obesity and COPD 2–3 D, in addition to similar COPD therapy, for the treatment of NASH, instead of essential fatty acids complex, received antral at a dose of 200 mg 3 times daily and, additionally, policosanol at a dose of 20 mg after the dinner for 30 days. The comparison group consisted of 30 apparently healthy individuals. **Results.** The proposed therapy with antral reduced the intensity of lysis of azoalbumin, azocasein and azocol in patients of group O2: at day 30, the decrease was 1.3, 1.2 and 1.6 times ($p < 0.05$), respectively, in patients of the group O1: on day 30, the decrease was 1.2, 1.2 and 1.6 times ($p < 0.05$), respectively, compared to the pre-treatment values. In the group C, the values decreased less intensively ($p < 0.05$): only the azocol values were likely to change — 1.3 times ($p < 0.05$) with the presence of a significant difference with the groups O1 and O2 ($p < 0.05$). **Conclusions.** The combined administration of antral for 30 days resulted in a significant correction of proteinase-inhibitory homeostasis in patients with NASH associated with obesity and COPD, which was accompanied by a significant decrease in endotoxemia ($p < 0.05$) and damaging effect of systemic proteolysis ($p < 0.05$).

Keywords: non-alcoholic steatohepatitis; chronic obstructive pulmonary disease; proteolysis; endotoxemia

Introduction

Over the last few years, there has been an explosive interest of the scientific community in non-alcoholic fatty liver disease (NAFLD) and its progressive stage — non-alcoholic steatohepatitis (NASH) due to their widespread among the population of economically developed countries with

a growing trend in Ukraine [1–3]. In the USA, the number of cases of NAFLD is projected to reach 100.9 million people (35 %) by 2030, and the proportion of NASH among these patients will increase to 27 % [4]. Unfortunately, in Ukraine, there is no systematic data on the prevalence of NASH that makes it difficult to formulate a prognosis, but

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Для кореспонденції: Гринюк Ольга Євгенівна, аспірант кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, ВДНЗ України «Буковинський державний медичний університет», Театральна пл., 2, м. Чернівці, 58002, Україна; факс: (0372) 55-37-54; e-mail: hrinyuk.olha@gmail.com; контактний тел.: +38 (097) 188 17 84.

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we can definitely speak of a heavy economic burden and an increase in the number of patients with liver cirrhosis, terminal stages of the disease, requiring transplantation, and with hepatocellular carcinoma.

The experience of treating NASH is still small, so the therapy has not yet been developed in detail. The use of drugs with different mechanisms of action is investigated. There are known results from some studies of predominantly uncontrolled or descriptive nature, as well as small-scale randomized controlled (pilot) trials of several drugs, most of which are based on morphological data [5–8]. Researchers emphasize the reduction (arresting) of laboratory and morphological features of NASH activity [9, 10], but the results of pharmacotherapy are ambiguous. Despite the increase in the comorbidity of NASH and chronic obstructive pulmonary disease (COPD), there is a need to conduct studies regarding general mechanisms of development and burden interaction of these nosologies with the development of new correction methods.

According to a number of studies on the use of antral, the remedy promotes the restoration of glycogen and protein-synthesizing function of the liver, improves phospholipid synthesis, activates cytochrome system, stimulates tissue respiration processes, improves energy supply and functioning of hepatocyte monooxygenase system, contributing to the reduction of endotoxemia intensity [11, 12]. By inhibiting cyclooxygenase and reducing the synthesis of prostaglandins and other mediators of inflammation, antral exerts its anti-inflammatory effect, inhibiting the processes of free radical oxidation and enhancing the processes of neutralization of free radicals, leading to a decrease in the severity of cytolytic syndrome that prevents the destruction of hepatocytes and reduces the intensity of the inflammatory process in the bronchi [13].

In Ukraine, a new phytopreparation has appeared, which improves the lipid spectrum of the blood and has an antioxidant effect protecting low-density lipoprotein cholesterol from destruction by free radicals, reducing hypertriglyceridemia, suppressing excessive platelet aggregation and improving the effectiveness of statin therapy in combined use — phytostatin, which is a mixture of fatty alcohols extracted from the waxy mass of sugar cane [14].

Purpose. Determination of the intensity of systemic proteolysis and endogenous intoxication before treatment and the efficacy of the use of antral in patients with NASH against the background of obesity, depending on the comorbidity of COPD.

Material and methods

Seventy-six patients with NASH, grade 1 obesity and COPD 2–3 D were screened and divided into 3 groups according to the treatment received. Before treatment, the average activity of cytolytic syndrome (the activity of alanine aminotransferase) was $(1.440 \pm 0.011) \mu\text{mol/h} \cdot \text{l}$. The control group (group C) consisted of 23 patients receiving basic treatment for NASH (essential fatty acids complex 300 mg 2 capsules 3 times daily) for 30 days and baseline COPD therapy (budesonide 160 $\mu\text{g/d}$ + formoterol fumarate 4.5 $\mu\text{g/d}$) by inhalation 2 times a day for

30 days; ipratropium/fenoterol (250/500 $\mu\text{g/ml}$) by inhalation with a nebulizer twice a day, azithromycin 500 mg once per day for 10 days. Twenty-five patients (group 2 — primary, O1), in addition to similar COPD therapy, for the treatment of NASH, instead of essential fatty acids complex, received antral at a dose of 200 mg 3 times a day for 30 days. The third group (basic, O2) involving 28 patients with NASH, grade 1 obesity and COPD 2–3 D, in addition to similar baseline COPD therapy, for the treatment of NASH, instead of essential fatty acids complex, received antral at a dose of 200 mg 3 times daily and, additionally, policosanol at a dose of 20 mg after the dinner for 30 days. The mean age of the patients was (55.70 ± 3.22) years. The comparison group consisted of 30 apparently healthy individuals (AHI).

The diagnosis of NASH was made according to the unified clinical protocol approved by the order of the Ministry of Health of Ukraine No. 826 of 06.11.2014, in the presence of criteria for the exclusion of chronic diffuse liver disease of viral, hereditary, autoimmune or drug genesis as the cause of cytolytic, cholestatic, mesenchymal-inflammatory syndromes, and the results of ultrasonography with shear wave elastography, SteatoTest.

The diagnosis was established and the treatment for COPD was conducted following the clinical guidelines (MOH Order No. 555 of June 27, 2013, taking into account the recommendations of GOLD, 2019).

The obesity was diagnosed according to the classification of the WHO International Obesity Working Group (1997). The patients were subjected to measurements of height and body weight, their body mass index (BMI) was calculated according to the Kettle formula (1):

$$BMI = \text{mass (kg)} / \text{height}^2 \text{ (m)}. \quad (1)$$

The diagnosis of obesity was made with BMI higher than 30 kg/m^2 .

On admission to the hospital, the functional state of the liver was determined according to the approval list of activity of enzymes, markers of pigment and nitrogen metabolism, proteinogram, lipidogram, ionogram, and calculation of the de Ritis ratio. All the patients underwent anthropometry to determine BMI, waist circumference (WC), hip circumference (HC), and waist/hip index ($WHI = WC/HC$).

The intensity of endotoxemia was studied by the content of medium molecular weight peptides (MMWP) by the method of N.I. Gabrielyan at 254 and 280 nm. The proteolytic activity of blood plasma was studied using azoalbumin (AA) (lysis of low molecular weight proteins), azocasein (AC) (lysis of high molecular weight proteins), azocol (CLA) (collagen lysis) using standard reagent kits (Simko Ltd, Lviv).

Statistical analysis of the results was performed according to the type of study conducted and the types of numerical data obtained. The normality of the distribution was checked using the Lilliefors, Shapiro-Wilk tests and the method of direct visual evaluation of the histograms of the distribution of eigenvalues. Quantitative indicators that had a normal distribution are presented as mean (M) \pm standard deviation (S). For comparisons of data that had a normal

distribution, parametric tests were used, particularly, Student's t-test, Fisher's F-test. For statistical and graphical analysis of the obtained results Statistica for Windows software version 8.0 (StatSoft Inc., USA), Microsoft Excel 2007 (Microsoft, USA) were used.

Results

The analysis of systemic proteolysis indicators for treatment in patients with NASH, obesity and COPD indicates that they are significantly higher compared to AHI. Thus, the intensity of azoalbumin and azocasein lysis exceeded that of AHI by 1.4 times (4.15 ± 0.08 and 3.59 ± 0.03) E440/ml/h vs (2.91 ± 0.06 and 2.59 ± 0.05) E440/ml/h, respectively, compared to AHI, and the intensity of azocol lysis increased by 2.0 times (1.22 ± 0.05 vs 0.61 ± 0.04) E440/ml/h ($p < 0.05$). At the same time, patients with a comorbid course of NASH and COPD experienced a significant level of endogenous intoxication, which was established by blood levels of MMWP 254 and MMWP 280. In particular, the blood content of MMWP 254 was 1.8 times increased (0.43 ± 0.03) vs (0.240 ± 0.001) c.u./l, respectively), and MMWP 280 — by 2.0 times (0.51 ± 0.02) vs (0.260 ± 0.001) c.u./l compared to AHI ($p < 0.05$) (Table 1).

The analysis of the effect of antral complex therapy on the state of endotoxiosis and the proteinase-inhibitory system (Table 1) indicates a higher degree of efficacy in the groups of patients O1 and O2 since only these groups developed a significant decrease in the intensity of lysis of AA, AC, CLA ($p < 0.05$).

Thus, the maximum effect on the lysis intensity of AA, AC, and azocol was achieved using the therapy in patients of the group O2: on day 30, the decrease was 1.3 (from 4.13 ± 0.08) to (3.25 ± 0.03) E440/ml/h, 1.2 (3.54 ± 0.02) E440/ml/h, and 1.6 (1.22 ± 0.04) E440/ml/h times, respectively ($p < 0.05$),

compared with the values before treatment. The effect of treatment on patients in group O1 was also significant: on day 30, the decrease was 1.2 (3.57 ± 0.06) vs (4.12 ± 0.07) E440/ml/h, 1.2 (3.60 ± 0.03) vs (3.02 ± 0.10) E440/ml/h, and 1.6 (0.78 ± 0.01) vs (1.23 ± 0.06) E440/ml/h times, respectively ($p < 0.05$), compared with the values before treatment. In the group C, the decrease also occurred, but much slower and less intensive ($p < 0.05$) (Table 1): only the CLA indicator changed significantly — 1.3 times decreased (from 1.22 ± 0.05) to (0.93 ± 0.02) E440/ml/h ($p < 0.05$) compared with the values in the groups O1 (0.78 ± 0.01) and O2 (0.75 ± 0.01) E440/ml/h ($p < 0.05$).

In patients with NASH with COPD received the therapy programs containing antral, the degree of endogenous intoxication also reduced more effectively. Thus, in patients of groups O1 and O2, the blood levels of MMWP 254 decreased after treatment by 1.2 (from 0.42 ± 0.03) to (0.34 ± 0.01) c.u./l) and 1.3 (from 0.43 ± 0.04) to (0.32 ± 0.01) c.u./l) times, respectively ($p < 0.05$), and MMWP 280 — by 1.8 (from 0.52 ± 0.01) to (0.28 ± 0.01) c.u./l) and 2.0 (from 0.51 ± 0.02) to (0.27 ± 0.01) c.u./l) times, respectively ($p < 0.05$) with normalization of the values against 1.3 times (0.43 ± 0.03) vs (0.38 ± 0.02) c.u./l after the therapy) in the group C ($p < 0.05$) (Table 1). The complex therapy of patients with NASH associated with obesity and COPD which included antral in combination with policosanol helped to reduce the damaging effect on systemic proteolysis and endotoxiosis in patients with NASH, COPD and obesity.

Discussion

Detoxification function of the liver requires intensive aerobic metabolism to produce sufficient ATP in the mitochondria of hepatocytes, which leads to the constant formation of reactive oxygen species (ROS) [15]. It should be noted that damage to hepatocytes with the presence of in-

Table 1 — Indicators of intensity of systemic endotoxiosis, plasma proteolysis, collagenolysis in patients with non-alcoholic steatohepatitis accompanied by obesity and COPD in the dynamics of treatment (M ± m)

Values	AHI	Groups of patients with NASH, obesity and COPD					
		Group C (n = 23)		Group O1 (n = 25)		Group O2 (n = 28)	
		Before treatment	In 30 days	Before treatment	In 30 days	Before treatment	In 30 days
Azoalbumin lysis, E440/ml/h	2.91 ± 0.06	$4.15 \pm 0.08^*$	$3.60 \pm 0.07^*$	$4.12 \pm 0.07^*$	$3.57 \pm 0.06^{*,\#}$	$4.13 \pm 0.08^*$	$3.25 \pm 0.03^{*,\#,***}$
Azocasein lysis, E440/ml/h	2.59 ± 0.05	$3.59 \pm 0.03^*$	$3.43 \pm 0.12^*$	$3.60 \pm 0.03^*$	$3.02 \pm 0.10^{*,\#}$	$3.54 \pm 0.02^*$	$2.91 \pm 0.07^{*,\#}$
Azocol lysis, E440/ml/h	0.61 ± 0.04	$1.22 \pm 0.05^*$	$0.93 \pm 0.02^{*,**}$	$1.23 \pm 0.06^*$	$0.78 \pm 0.01^{*,\#,**}$	$1.22 \pm 0.04^*$	$0.75 \pm 0.01^{*,\#,**}$
MMWP 254, c.u./l	0.240 ± 0.001	$0.43 \pm 0.03^*$	$0.38 \pm 0.02^*$	$0.42 \pm 0.03^*$	$0.34 \pm 0.01^{*,\#,**}$	$0.43 \pm 0.04^*$	$0.32 \pm 0.01^{*,\#,**}$
MMWP 280, c.u./l	0.260 ± 0.001	$0.51 \pm 0.02^*$	$0.39 \pm 0.02^{*,**}$	$0.52 \pm 0.01^*$	$0.28 \pm 0.01^{*,\#,**}$	$0.51 \pm 0.02^*$	$0.27 \pm 0.01^{*,\#,**}$

Notes: group C (control) — patients with NASH who received essential fatty acids complex; group O1 (basic) — patients with NASH who received antral; group O2 — patients with NASH who received antral and phytostatin; * — the difference is probable compared with the AHI group ($p < 0.05$); ** — probable difference compared with the values before treatment ($p < 0.05$); # — probable difference compared with the values after treatment in patients of group C ($p < 0.05$); *** — probable difference compared with the values after treatment in patients of group O1 ($p < 0.05$) with the values in patients of group O2 ($p < 0.05$).

inflammation can significantly increase the intensity of free radical processes, both in each hepatocyte and in the organ as a whole. These processes further intensify under the conditions of hypoxia caused by lung damage [16]. Oxidative stress leads to an increase in the production of ROS and, as a consequence, the oxidative modification of proteins (OMP): their aggregation and fragmentation, which is accompanied by irreversible changes in the physicochemical and biological properties of the protein molecule. It is known from the existing literature on OMP processes that proteins in which their oxidative modification takes place are much easier to proteolysis [17].

During the study, we found a significant increase in proteolysis (lysis intensity of AC, AA, CLA) in the groups before treatment compared to the AHI group ($p < 0.05$). In our opinion, the activation of some proteolytic enzymes and their involvement in the processes of degradation of protein components are affected by lysosomal proteinases, which after being exposed to free radical oxidation of lipids and oxidative modification of proteins into cells are released from them upon their destruction. Peptide hydrolase released from cells catalyzes specific reactions of limited proteolysis and, in our view, activates inactive precursors of enzymes and isolates specific inhibitors of proteolysis [18–20].

Therefore, in case of NASH associated with obesity and comorbid COPD, the development of an imbalance of the protease-inhibitory system is caused by the uncontrolled elevation in the proteolytic activity of blood plasma.

The degree of endogenous intoxication is to depend not only on the severity and nature of inflammation in the lungs but also on the functional state of the hepatic detoxification system [21, 22], which coincides with the data of our study. A significant level of endotoxemia, which we established for blood levels of MMWP 254 and MMWP 280, was observed in patients with comorbid NASH, obesity and COPD compared with the AHI group ($p < 0.05$). There is no room for doubt the fact of the involvement of membrane destructive phenomena in hepatocytes, that makes it possible to correct this type of comorbidity using the drugs with a membrane-stabilizing effect. Antral exhibits such properties [23].

In the groups of patients who received antral for a hepatoprotective therapy (O1 and O2), the degree of endogenous intoxication decreased, there was a significant reduction in the intensity of lysis of AA, AC, and collagen ($p < 0.05$). Due to stimulation of β -oxidation of fatty acids and influence on the synthesis of phospholipids, antral improves energy processes in cells and arranges the functioning of monooxygenase systems, as a consequence of which the hepatocytes reduce the accumulation of fat, the degree of damage to hepatic cells decreases. There are also data on the effect of antral on immune regulation, namely the effect on T-helper cells and the decrease in the level of circulating immune complexes that contributes to the reduction of the expression of metabolic toxicosis [24]. Regarding the combination of antral with policosanol, we registered the best corrective effect on the proteolysis system, namely a probable decrease in the intensity of azoalbumin lysis ($p < 0.05$).

Prospects for further research in this direction is a further study of the effect of antral and policosanol on the dynamics of clinical, biochemical syndromes of NASH with comorbid COPD on day 60, 90 and 120 of administration, as well as to study the long-term effects of the course of treatment.

Conclusions

1. Patients with non-alcoholic steatohepatitis, obesity and COPD comorbidity showed a significant increase in the intensity of endogenous intoxication with accumulation of medium molecular weight peptides 254 and 280 in the blood (1.8 and 2.0 times, respectively; $p < 0.05$), which was accompanied by activation of proteolysis (1.4–2.0 times; $p < 0.05$).

2. Administration of hepatoprotector antral within 30 days led to a significant correction of the damaging effect on the proteolysis system in patients with NASH, obesity and COPD with a significant decrease in the blood content of azoalbumin, azocasein and collagenolytic activity ($p < 0.05$), accompanied by a significant decrease in endotoxemia ($p < 0.05$).

3. Improvements in the effectiveness of NASH and COPD treatment with combined administration of antral and policosanol on the state of proteolysis and endogenous intoxication have been registered by the intensity of azoalbumin lysis ($p < 0.05$).

Conflict of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Інтенсивність системного протеолізу та ендотоксикозу в динаміці лікування гепатопротекторами хворих на неалкогольний стеатогепатит на тлі ожиріння за коморбідності з хронічним обструктивним захворюванням легень

Резюме. Актуальність. Поширеність захворюваності на неалкогольний стеатогепатит (НАСГ) та хронічне обструктивне захворювання легень (ХОЗЛ) набуває глобального значення серед населення економічно розвинених країн світу з тенденцією зростання і в Україні. **Мета дослідження:** визначення інтенсивності системного протеолізу та ендогенної інтоксикації до лікування та в динаміці застосування гепатопротекторів у хворих на НАСГ на тлі ожиріння та коморбідного ХОЗЛ. **Матеріали та методи.** 76 хворих на НАСГ, ожиріння І ст. та ХОЗЛ 2–3 D пройшли обстеження та були розподілені на 3 групи залежно від призначеного лікування. До першої групи — контрольної (К) — увійшли 23 хворі, які отримували базисну терапію НАСГ (комплекс есенціальних фосфоліпідів 300 мг по 2 капсули 3 рази на

день) упродовж 30 днів та базисну терапію ХОЗЛ. 25 хворих (група 2 — основна, О1), крім аналогічної терапії ХОЗЛ, для лікування НАСГ замість комплексу есенціальних фосфоліпідів отримували антраль 200 мг 3 рази на день упродовж 30 днів. Третя група (основна, О2) — 28 хворих, крім аналогічної терапії ХОЗЛ, для лікування НАСГ замість комплексу есенціальних фосфоліпідів отримували антраль 200 мг 3 рази на день та додатково полікозанол 20 мг після вечері впродовж 30 днів. Групу порівняння становили 30 практично здорових осіб. **Результати.** Запропонована терапія антралем вплинула на зменшення інтенсивності лізису азоальбуміну, азоказеїну та азоколу у хворих групи О2: на 30 день зазначений показник знизився відповідно в 1,3; 1,2 та 1,6 рази ($p < 0,05$), у хворих групи О1: на 30-й день — в 1,2; 1,2 та

1,6 раза відповідно ($p < 0,05$) порівняно з величинами до лікування. У групі К зниження відбувалося менш інтенсивно ($p < 0,05$): вірогідно змінювався лише показник лізису азоколу — знизився в 1,3 раза ($p < 0,05$) за наявності вірогідної різниці з показниками у групах О1 та О2 ($p < 0,05$). **Висновки.** Призначення антраля упродовж 30 днів призвело до істот-

ної корекції протеїназо-інгібіторного гомеостазу у хворих на НАСГ із ожирінням та ХОЗЛ, що супроводжувалось вірогідним зниженням ендотоксикозу ($p < 0,05$) та ушкоджувальної дії системного протеолізу ($p < 0,05$).

Ключові слова: неалкогольний стеатогепатит; хронічне обструктивне захворювання легень; протеоліз; ендотоксикоз

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Интенсивность системного протеолиза и эндотоксикоза в динамике лечения гепатопротекторами больных неалкогольным стеатогепатитом на фоне ожирения при коморбидности с хроническим обструктивным заболеванием легких

Резюме. Актуальность. Распространенность заболеваемости неалкогольным стеатогепатитом (НАСГ) и хронической обструктивной болезнью легких (ХОБЛ) приобретает глобальное значение среди населения экономически развитых стран мира с тенденцией роста и в Украине. **Цель исследования:** определение интенсивности системного протеолиза и эндогенной интоксикации до лечения и в динамике применения антраля у больных НАСГ на фоне ожирения и коморбидной ХОБЛ. **Материалы и методы.** 76 больных НАСГ на фоне ожирения I ст. и ХОБЛ 2–3 D прошли обследование и были распределены на 3 группы в зависимости от назначенного лечения. В первую группу — контрольную (К) — вошли 23 больных, получавших базисную терапию НАСГ (комплекс эссенциальных фосфолипидов 300 мг по 2 капсулы 3 раза в день) на протяжении 30 дней и базисную терапию ХОБЛ. 25 больных (группа 2 — основная, О1), кроме аналогичной терапии ХОБЛ, для лечения НАСГ вместо комплекса эссенциальных фосфолипидов получали антраль 200 мг 3 раза в день на протяжении 30 дней. Третья группа (основная, О2) — 28 больных, кроме аналогичной терапии ХОБЛ, для лечения НАСГ вместо комплекса эссенциаль-

ных фосфолипидов получали антраль 200 мг 3 раза в день и дополнительно поликозанол 20 мг после ужина в течение 30 дней. Группу сравнения составили 30 практически здоровых лиц. **Результаты.** Предложенная терапия антралем повлияла на уменьшение интенсивности лизиса азоальбумина, азоказеина и азокола у больных группы О2: на 30 день указанный показатель снизился соответственно в 1,3; 1,2 и 1,6 раза ($p < 0,05$), у больных группы О1: на 30 день — соответственно в 1,2; 1,2 и 1,6 раза ($p < 0,05$) по сравнению с данными до лечения. В группе К снижение происходило менее интенсивно ($p < 0,05$): достоверно менялся только показатель азокола — снизился в 1,3 раза ($p < 0,05$) при наличии достоверной разницы с показателями в группах О1 и О2 ($p < 0,05$). **Выводы.** Назначение антраля на фоне базисной терапии в течение 30 дней привело к существенной коррекции протеиназо-ингибиторного гомеостазу у больных НАСГ с ожирением и ХОБЛ, сопровождалось достоверным снижением эндотоксикоза ($p < 0,05$) и повреждающего действия системного протеолиза ($p < 0,05$).

Ключевые слова: неалкогольный стеатогепатит; хроническая обструктивная болезнь легких; протеолиз; эндотоксикоз