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ЭФФЕКТИВНОСТЬ КОМБИНИРОВАННОЙ ТЕРАПИИ БОЛЬНЫХ С ОБОСТРЕНИЕМ ХРОНИЧЕСКОГО ОБСТРУКТИВНОГО ЗАБОЛЕВАНИЯ ЛЁГКИХ

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Проведена оценка эффективности применения фенспирида и антигомотоксических препаратов в комбинации со стандартной терапией больных с хроническим обструктивным заболеванием лёгких (ХОБЛ) I–II стадии в период обострения с учётом состояния реологии крови и иммунной системы. Нарушение реологических характеристик крови отмечено у 2/3 больных ХОБЛ I–II стадии в фазе обострения. У больных ХОБЛ выявлены три типа реакций системного иммунитета: гиперергическая (5 показателей и более увеличены на $\geq 20\%$), гипоергическая (5 показателей и более уменьшены на $\geq 20\%$), некоторые иммунные нарушения (от 1 до 4 показателей уменьшены на $\geq 20\%$), что позволяет дифференцированно проводить терапию фенспиридом и антигомотоксическими препаратами.

Ключевые слова: иммунитет, реология крови, фенспирид, антигомотоксические препараты, хроническое обструктивное заболевание лёгких.

THE EFFECTIVENESS OF COMBINATION THERAPY IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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This article provides an assessment of the effectiveness of fenspiride and antihomotoxic drugs in combination with standard therapy in patients with chronic obstructive pulmonary disease (COPD) stage I-II with acute exacerbation taking into account the rheology of blood and immune system. Violation of the rheological properties of blood in 2/3 patients with COPD stage I–II in the acute phase was observed. There are three types of reactions of systemic immunity: hyperergic (5 or more indicators increased by $\geq 20\%$), hypoergic (5 or more indicators reduced by $\geq 20\%$) and certain immune disorders (1 to 4 indicators reduced by $\geq 20\%$) In patients with COPD were identified, that allows to carry out differentiated therapy with fenspiride and antihomotoxic drugs.

Key words: immunity, blood rheology, fenspiride, antihomotoxic drugs, COPD.

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INFLUENCE OF THE TRADITIONAL THERAPY AND ITS COMBINATION WITH THIOTRIAZOLIN® ON DYNAMICS OF THE ENDOGENOUS INTOXICATION INDICATORS, CYTOLOGICAL COMPOSITION OF SPUTUM AND ADAPTIVE RESPONSES OF THE PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

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The article presents the problem of treatment rates improvement of the patients with community-acquired pneumonia as a result of inclusion of Thiotriazolin® metabolic correction and

analysis of the clinical treatment rates in the complex of therapeutic measures. Inclusion of Thiotriazolin® in the treatment complex provided faster normalization of sputum cytogram, significantly reduced the level of the endogenous intoxication, which led to the increase in the number of favorable adaptive responses of the organism, more significantly than the traditional therapy, reduced the intensity of the inflammatory response in the lungs and reduced the time of elimination of the clinical disease.

Key words: community-acquired pneumonia, endogenous intoxication, cytological composition of sputum, adaptive responses of the organism, Thiotriazolin®.

Introduction. Community-acquired pneumonia (CAP) is one of the most widely-spread and dangerous infectious diseases of people, which remains the important medical and social problem caused by high rates of morbidity and mortality in the XXI century [17, 18].

The inability of the adaptive mechanisms to counter the adverse factors in the environment and the internal environment contributes to appearance of the pathological process in the respiratory organs [9]. The organism responds to the sum of these factors by formation of the favorable (calm and high activation) and adverse (stress, re-activation, defective adaptation) adaptive responses. The latter ones lead to more severe course of the disease [2].

There is evidence that the type of the general non-specific adaptive response can be a criterion for the response of the patient's organism to inflammation in the pulmonary tissue, as well as the indicator of the treatment rates [12, 15].

It is known that pneumonia is always characterized by the disorder of the metabolic homeostasis and endotoxemia that leads to the development of tissue hypoxia, which is one of the important links in the pathogenesis of the endogenous intoxication syndrome, the course of which deepens the depression of the functions of the natural detoxification and excretion organs [4]. In order to normalize these disorders under these conditions the organism needs pharmacological support, for which the standard treatment with antibiotics may not be sufficient.

At present one of the most effective ways of influencing the metabolic homeostasis is the use of Thiotriazolin®. Many clinical and experimental studies have demonstrated its effectiveness [3, 5, 6, 10, 13]. It has been shown that Thiotriazolin® has a regulatory effect on all types of metabolism in the organism, possesses detoxification, antioxidant, membrane stabilizing, and immunomodulatory properties, as well as improves the reparative processes [13].

In our opinion, the use of Thiotriazolin® in the complex treatment of the patients with CAP will optimize the results of treatment, namely, reduce the time of elimination of the clinical disease and reduce the period of the patient staying in the hospital.

The purpose of the study is to increase the treatment rates of the patients with community-acquired pneumonia and to study the dynamics of the indicators of endogenous intoxication, cytological composition of sputum and adaptive responses of the organism by inclusion of the metabolic correction of Thiotriazolin® in the complex of therapeutic measures.

Materials and methods. A complete clinical, laboratory, X-ray examination of 120 patients with CAP of the 3rd clinical group which were treatment in the therapeutic department of the city clinical hospital of emergency medical care in Vinnytsia was conducted. There were 61 (50,8 %) men, and 59 (49,2 %) women. The age of the examined patients ranged from 18 to 68 and was (56,4 ± 1,6) years.

The control (II) group included 50 (41,6 %) patients who received the traditional therapy, according to the order of the Ministry of Health of Ukraine N 128 of 19.03.2007 [7]. The causal treatment involved the use of the empirical therapy of cephalosporin of the 3rd generation – Cefotaxime 1.0 intramuscularly twice a day and macrolide – Clarithromycin 500 mg twice a day for seven days. The mucolytic drugs were prescribed along with the causal drugs – Ambroxol 30 mg three times a day p. o.

Accordingly, the I group consisted of 70 (58,4 %) patients who, along with the baseline therapy, were additionally administered the 2,5 % solution of Thiotriazolin®

4 ml (100 mg) per day – three days intravenously per 200 ml of physiological solution, then seven days intramuscularly. The groups were represented according to the age, sex, and severity of the clinical course.

The evaluation of the therapy rates in the I and II groups was carried out taking into account the dynamics of the indicators of the endogenous intoxication: leukocyte index of intoxication (LII) [8], average molecules level (AML) [17], sorption erythrocytes capacity (SEC) [13]. The cytological composition of sputum of the patients with CAP who had cough with sputum was also investigated. According to Garkavi's method, the adaptive responses of the organism were detected [2]. The clinical therapy rates were determined by the analysis of the complex of dynamics of the clinical and laboratory data, adaptive responses of the organism to the treatment, and on the 3rd and 10th day after the prescribed treatment.

The X-ray examination of the thoracic organs was performed for all patients. The treatment was considered clinically effective if after completion of the study the symptoms completely disappeared (recovery) or the symptom expression and X-ray disease signs significantly reduced (improvement). The obtained data were processed using the methods of variation statistics with the calculation of the average values according to the known formulas, errors of averages. The accuracy of the differences was determined by Student's criterion (*t*) and was evaluated using the confidence probability (*P*). The differences were considered to be significant at $P < 0,05$.

The results and their discussion. The significant level of the endogenous intoxication was detected by the patients of the I and II groups, as evidenced by the probable increase in LII, AML, SEC ($P < 0,001$) compared to the normative indicators of the practically healthy persons (Table 1).

Table 1. Dynamics of the endogenous intoxication indicators of the patients with community-acquired pneumonia

Indicators	Regulatory indicators of healthy persons	I group (<i>n</i> = 70)			II group (<i>n</i> = 50)		
		Before treatment	3 rd day	10 th day	Before treatment	3 rd day	10 th day
LII, c. u.	0,3 ± 0,5	1,46 ± 0,05	0,87 ± 0,05*	0,44 ± 0,02*	1,41 ± 0,07	1,57 ± 0,02	1,21 ± 0,07
AML ₂₅₄ , c. u.	0,24 ± 0,01	0,431 ± 0,023	0,284 ± 0,004*	0,201 ± 0,005*	0,463 ± 0,026	0,501 ± 0,032	0,341 ± 0,023
SEC, %	37,1 ± 1,4	66,8 ± 1,2	45,1 ± 1,1*	37,4 ± 0,3*	66,7 ± 1,5	72,7 ± 1,4	55,9 ± 1,6

*The significant difference compared with the same indicator of the II group ($P < 0,001$).

The decrease in the intensity of the endogenous intoxication indicators was accompanied by the positive dynamics of the clinical course of CAP of the patients. In the group of the patients receiving the traditional treatment, the leukocyte index of intoxication on the 3rd day of pharmacotherapy increased by 11,3 % ($P > 0,05$), and in the group of the patients receiving additionally Thiotriazolin[®], it vice versa – decreased by 40,4 % ($P < 0,001$). The dynamics of the studied index on the 10th day in both groups of the patients was similar. In particular, in the II group, LII decreased by 16,5 % ($P < 0,01$) while in the I group – in more than 3 times, and at the end of the study period it was (0,44 ± 0,02) c. u. ($P < 0,001$).

The dynamics of the molecules of the average mass was similar to the dynamics of LII. So, if in the II group of the patients on the 3rd day of the treatment, AML₂₅₄ increased by 8,9 % ($P > 0,05$), then in the I group it decreased by 53,6 % ($P < 0,001$). During the next 7 days of the treatment reduction of this indicator was observed in both groups. In 10 days the greatest and significantly better dynamics of the analyzed index was preserved in the group of the patients receiving the combination therapy of antibiotics with Thiotriazolin[®]. The difference between the value of AML₂₅₄ before treatment and its value on the 10th day of the pharmacotherapy made up more than 2 times ($P < 0,001$), whereas in the group of the patients receiving only antibacterial agents it was only 35 % ($P < 0,001$).

The analysis of the dynamics of SEC indicators showed that in the group of the patients receiving the standard therapy, the level of SEC remained high on the 3rd day of the treatment, having increased by 9 % ($P < 0,05$), and of the persons treated with the inclusion of Thiotriazolin® this indicator decreased by 33 % ($P < 0,001$). On the 10th day in the II group this indicator decreased by 16,2 % ($P < 0,001$), and in the I group – by 44,9 % ($P < 0,001$).

It is of importance to note that on the 10th day of the treatment the values of LII, AML₂₅₄, SEC of the patients of the I group probably did not differ from the corresponding indicators of the normal values ($P > 0,05$).

35 (70 %) patients in the II group and 50 (71,4 %) patients in the I group had productive cough before hospitalization. The analysis of the cytological composition of sputum showed that in the group of the patients receiving the standard therapy in 63,3 % of the cases there were the segmental neutrophils and in 11,5 % of the cases there were the epithelial cells detected. And 65,4 % of the patients of the I group had the segmental neutrophils, and 10,5 % of them had the epithelial cells.

Regardless of the scheme used in the treatment of the patients with CAP there was redistribution of the cellular sputum (Table 2).

Table 2. Dynamics of the cytological composition of sputum of the patients with community-acquired pneumonia during the treatment

Cells	Initial level of cells, %	3 rd day		10 th day	
		%	Δ %	%	Δ %
<i>I group (n = 70)</i>					
Neutrophils	63,30 ± 3,34	44,5 ± 2,4*	18,8*	26,3 ± 1,6**	37**
Epithelial cells	11,50 ± 0,96	24,9 ± 0,9**	14,4**	43,8 ± 1,7**	32,3**
<i>II group (n = 50)</i>					
Neutrophils	65,40 ± 2,81	55,7 ± 4,1	9,7	45,9 ± 3,1	19,5
Epithelial cells	10,5 ± 1,6	16,0 ± 2,5	4,5	20,5 ± 2,5	10

*The probable difference at $P < 0,05$ in comparison with the II group. **The probable difference at $P < 0,001$ in comparison with the II group.

Already on the 3rd day of their staying in the hospital, compared to the initial indicators, there was a statistically significant decrease of the number of the neutrophils by 1,47 times ($P < 0,05$) and increase of the epithelial cells in 2,36 times ($P < 0,001$) in the sputum of the patients receiving additionally Thiotriazolin®. In the group of the patients in the II group the level of the segmental neutrophils in the sputum decreased only in 1,14 times ($P > 0,05$), and the level of the epitheliocytes – increased in 1,39 times ($P > 0,05$). On the 10th day of the treatment there was a significant (in 2,49 times) reduction of the content of the segmental neutrophils ($P < 0,001$) and increase (4,17 times) of the epithelial cells ($P < 0,001$) by the cytological study of the sputum of the patients of the I group. In the group of the patients with CAP, receiving the traditional treatment, the dynamics of the above indicators was less noticeable. Thus, on the 10th day of the study, the number of the neutrophils in the sputum decreased in 1,38 times, and the number of the epithelial cells increased only in 1,78 times ($P < 0,001$).

Almost every third patient in the study group noted the presence of adverse adaptive responses (re-activation, acute and chronic stress). As to the favorable adaptive responses (calm and high activation reactions), they were also observed at almost the same frequency (51,9 % of the patients of the II group and 48,1 % of the I group).

We noticed some changes in the nature of the adaptive responses of the organism. In particular, the percentage of the favorable responses on the 3rd day of the treatment in the II group increased only from 38 % to 40 %, and on the 10th day decreased from 40 % to 32 % ($P > 0,05$). At the same time, in the I group there was a significant reduction in the number of the adverse responses from 38,6 % to 21,4 % on the 3rd day of hospitalization ($P < 0,01$), and from 21,4 % to 5,7 % on the 10th day ($P < 0,001$).

That is, there was the transition of tense and inferior responses into the zone of the adaptive responses favorable for the organism.

In the group of the patients receiving the complex treatment, in comparison with the patients of the II group there was a more significant increase of the favorable responses. The additional prescription of Thiotriazolin® increased the proportion of the patients with the favorable adaptive responses from 51,9 % to 69,9 % already on the 3rd day and from 69,9 % to 91,4 % ($P < 0,01$) on the 10th day. In the II group on the 3rd day of staying in the hospital the number of the favorable adaptive responses increased only from 48,1 % to 54 %, and on the 10th day – from 54 % to 62 % ($P > 0,05$).

One of the most important criteria for the treatment of the patients with CAP is the positive dynamics of X-ray pattern. The residual X-ray changes in the form of inter-particle and pleurodiopharmaeal conjunctions and post-pneumonia fibrosis were detected in 28 % of the patients in the I group and 40 % – of the II group. Regarding the clinical treatment rates, the recovery was observed in 72 % of the patients in the I group and only 60 % – of the II group.

There are also certain differences in the terms of hospitalization of the patient. Staying in the hospital for the patients receiving only the baseline therapy made up on the average ($14,10 \pm 0,48$) days, and the patients who were prescribed the comprehensive treatment with Thiotriazolin® inclusion – ($10,90 \pm 0,32$) days or was by 29,3 % less ($P < 0,001$).

Summarizing the data obtained, it can be quite argued that the use of the baseline therapy in combination with Thiotriazolin®, in comparison with the traditional treatment of CAP, provides faster decrease of the indicators (LII, AML₂₅₄, SEC) of the endogenous intoxication. The similarity of the results was demonstrated in the scientific studies on the endogenous intoxication of the complicated pneumonia of newborns [13]. In particular, the use of Thiotriazolin® reduced the duration of toxicosis, fever, effectively prevented the development of cells energy failure, in particular erythrocytes, and increased their sorptive and metabolic detoxification capabilities.

The above data suggest that the use of Thiotriazolin® in the complex treatment of the patients with CAP promotes the faster normalization of the sputum cytogram, which was presented by decrease in the number of the neutrophils in 2,49 times and increase of the epitheliocytes in 4,17 times, which is the clinically beneficial sign of the course of the disease [8]. The reasons for these changes, in our opinion, are anti-inflammatory and immunomodulatory effects of the drug [3, 6, 10, 14].

The additional prescription of Thiotriazolin® also provided the increase in favorable responses preceding the regression of the disease. The similar properties of Thiotriazolin® were obtained in the treatment of children of the different ages with community-acquired pneumonia [19].

In the course of the study it was found that the effectiveness of the pharmacotherapy varied significantly depending on the treatment. The traditional therapy of the patients with CAP significantly improved the sputum cytogram, reduced the level of the endogenous intoxication, increased the number of the favorable adaptive responses of the organism, and also positively influenced the course of the inflammatory process in the lungs. The inclusion of Thiotriazolin® in the complex treatment provided faster normalization of the sputum cytogram, significantly reduced the level of the endogenous intoxication, which led to the increase in the number of the favorable adaptive responses of the organism, more significantly than the traditional therapy reduced the intensity of the inflammatory response in the lungs and reduced the time of elimination of the clinical disease.

Conclusions. 1. The traditional pathogenic therapy of the patients with CAP on the 10th day of the treatment reduces the indices of the endogenous (LII 16,5 %, AML₂₅₄ 35 %, SEC by 16,2 %) intoxication, improves the cytogram (the number of the neutrophils decreased in 1,38 times, the number of the epithelial cells increased in 1,78 times) of sputum and increases the number of the favorable adaptive responses of the organism by 32 %. 2. Inclusion of Thiotriazolin® in the complex treatment of the patients with CAP in the daily dose of 100 mg for 10 days of the treatment not

only more rapidly reduced the indicators of the endogenous intoxication (LII more than 3 times, AML₂₅₄ more than 2 times, SEC by 44,9 %), but also contributed to the faster improvement of the sputum cytogram (the number of the neutrophils decreased by 2,49 times, the number of the epithelial cells increased by 4,17), increased the proportion of the patients with the favorable responses up to 91,4 %, and shortened the time of elimination of the clinical disease. 3. Determination of the type of the general non-specific adaptive responses of the organism, the dynamics of the indicators of the endogenous intoxication and the cytological composition of sputum can be the criteria for the treatment rates.

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**ВПЛИВ ТРАДИЦІЙНОЇ ТЕРАПІЇ ТА ЇЇ ПОЄДНАННЯ З ТІОТРИАЗОЛІНОМ®
НА ДИНАМІКУ ПОКАЗНИКІВ ЕНДОГЕННОЇ ІНТОКСИКАЦІЇ, ЦИТОЛОГІЧНОГО
СКЛАДУ МОКРОТИННЯ ТА АДАПТАЦІЙНИХ РЕАКЦІЙ ОРГАНІЗМУ У ХВОРИХ
НА НЕГОСПІТАЛЬНУ ПНЕВМОНІЮ**

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У статті розглянуто проблему підвищення ефективності лікування хворих на негоспітальну пневмонію під впливом включення до комплексу лікувальних заходів метаболічного коректора Тіотриазоліну® та аналізу клінічної ефективності лікування. Включення до комплексу лікування Тіотриазоліну® забезпечувало швидшу нормалізацію цитограми мокротиння, достовірне зменшення рівня ендогенної інтоксикації, що приводило до збільшення кількості сприятливих адаптаційних реакцій організму, більш суттєве, ніж під впливом традиційної терапії, зниження інтенсивності запальної реакції в легенях та скорочення терміну усунення клінічних проявів хвороби.

Ключові слова: негоспітальна пневмонія, ендогенна інтоксикація, цитологічний склад мокротиння, адаптаційні реакції організму, Тіотриазолін®.

**ВЛИЯНИЕ ТРАДИЦИОННОЙ ТЕРАПИИ И ЕЁ СОЧЕТАНИЕ С ТИОТРИАЗОЛИНОМ®
НА ДИНАМИКУ ПОКАЗАТЕЛЕЙ ЭНДОГЕННОЙ ИНТОКСИКАЦИИ,
ЦИТОЛОГИЧЕСКОГО СОСТАВА МОКРОТЫ И АДАПТАЦИОННЫХ РЕАКЦИЙ
ОРГАНИЗМА У БОЛЬНЫХ НЕГОСПИТАЛЬНОЙ ПНЕВМОНИЕЙ**

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В статье рассмотрена проблема повышения эффективности лечения больных негоспитальной пневмонией в результате включения в комплекс лечебных мероприятий метаболического корректора Тиотриазолина® и анализа клинической эффективности лечения. Включение в комплекс лечения Тиотриазолина® обеспечивало более быструю нормализацию цитограммы мокроты, достоверно уменьшало уровень эндогенной интоксикации, что приводило к увеличению количества благоприятных адаптационных реакций организма, более существенно, чем традиционная терапия, снижало интенсивность воспалительной реакции в лёгких и способствовало сокращению сроков устранения клинических проявлений болезни.

Ключевые слова: негоспитальная пневмония, эндогенная интоксикация, цитологический состав мокроты, адаптационные реакции организма, Тиотриазолін®.

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**ЕФЕКТИВНІСТЬ ТА БЕЗПЕЧНІСТЬ ІНТРАТЕКАЛЬНОГО ВВЕДЕННЯ
МОРФІНУ ГІДРОХЛОРИДУ ДЛЯ ЛІКУВАННЯ ХРОНІЧНОГО
БОЛЬОВОГО СИНДРОМУ У ХВОРИХ НА ОНКОЛОГІЧНІ
ЗАХВОРЮВАННЯ В ТЕРМІНАЛЬНІЙ СТАДІЇ**

Відділення анестезіології та інтенсивної терапії клініки «ЛІСОД»
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Біль – одна з найпоширеніших причин звернення пацієнтів до лікаря. Якщо біль тривалий, він може не лише призвести до фізичної неповноцінності, а й спричинити емоційний, психологічний тиск на пацієнтів та їхнє оточення. Хронічний біль надзвичайно поши-