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EFFECT OF LIPIN ADMINISTRATION IN A COMPREHENSIVE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA ASSOCIATED WITH COVID-19

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Abstract

The article describes the experience of practical use of Ukrainian drug Lipin (phosphatidylcholine (lecithin)) for the treatment of patients with pneumonias associated with COVID-19. The drug does not have any analogues at the market of phosphatidylcholines, possesses a strong anti-hypoxic action, promotes oxygen diffusion rate from the lungs into the blood and from the blood to the tissues, normalizes the processes of tissue respiration, restores functional activity of the endothelial cells, and improves microcirculation and rheological blood properties.

Keywords: pneumonia, COVID-19, treatment, phosphatidylcholine

Introduction

A considerable increase of pneumonia sickness rate during the epidemiological season 2020-2021 is caused by a number of circumstances, and the main of them is unexpected epidemics of coronavirus disease (COVID-19) in Ukraine and in the whole world. A severe course of COVID-19, complicated by acute respiratory distress-syndrome or SARS CoV-2-associated pneumonia, in some cases has an unfavorable prognosis concerning recovery and even life. In addition to complications by viral and viral-bacterial pneumonias COVID-19 is known to be associated with acquired immune deficiency, reduced surfactant synthesis due to affliction of type II alveolocytes with SARS CoV-2 virus, development of progressing respiratory failure, decrease of the blood rheological properties, inhibition of fibrinolysis, increased clot formation, lesions of the cardiovascular, excretory, nervous systems and the liver, and more intensive fibrosis of the lungs. Therefore, in management of patients with SARS CoV-2-associated pneumonia the above mentioned chains of SARS CoV-2 pathogenic influence should be considered and the effect of drugs able to produce a positive action on pneumonia clinical course should be learnt.

Several years ago the plant «Biolik» (Kharkiv) presented the drug Lipin-Biolik on the Ukrainian pharmaceutical market – collaboration with the Institute of Pharmacology and Toxicology, the Academy of Sciences of Ukraine. It is an original pharmacological agent possessing membrane protective, anti-hypoxic and antioxidant properties [2]. The active principle of Lipi-Biollik is phosphatidylcholine (lecithin-standard (in recalculation to lecithin – 500 mg)). It belongs to phospholipids in a freeze dried form for emulsion. Their molecules are the major lipid components of the cellular membranes, their universal "building material" [1, 2].

Since its discovery in the XIX century phosphatidylcholine has been considered as the main structural lipid. Though the data obtained for the last five years are indicative of the fact that phosphatidylcholine performs a number of functions [3-7]. Phosphatidylcholine as one of the main constituents of the lung surfactant possesses anti-inflammatory action and regulates activity of the alveolar macrophages. It should be noted that stability disorders of the surfactant system plays an important role in pathogenesis of many pulmonary diseases [8]. The value of Lipin is that its active principle is not only a universal "building material" for the organs and tissues of our body, but a factor to normalize many metabolic processes. The drug has anti-hypoxic action, promotes more rapid rate of oxygen diffusion from the lungs to the blood and from the blood into the tissues, normalizes the processes of tissue respiration, renews functional activity of the endothelial cells, improves microcirculation and rheological blood properties [9]. Moreover, it inhibits the processes of lipid peroxide oxidation (LPO) in the blood and tissues, maintains activity of the antioxidant systems (AAS) in the body, produces membrane protective effect, performs the function of non-specific detoxicant, and increases nonspecific immunity [10]. The drug possesses broncholytic, mucolytic and antioxidant action [11,12]. Lipin is used with syndromes of acute and chronic respiratory failure of various geneses among adults and children. The drug is not toxic and does not disturb functional state of the organs and systems of the body [13].

The results of clinical studies confirm that Lipin-Biolik is an effective pathogenic therapeutic agent producing a positive effect on the pathophysiological chains with respiratory failure syndrome among patients of different ages [14]. Administration of Lipin-Biolik decreases lethal outcome with respiratory failure syndrome [15]. At the same time, analysis of Lipin-Biolik effect in a comprehensive treatment of SARS CoV-2-associated pneumonias has not been made yet, and it confirms the topicality of our research.

Objective to investigate the effect of Lipin-Biolik therapy on a clinical course of moderate pneumonia associated with COVID-19 as a supplement to the basic therapy at the department of pulmonology.

Methods

94 case histories of institutional patients who were treated at the Department of Pulmonology, Chernivtsi Regional Clinical Hospital during 2020-2021 were examined. The patients were divided into two groups: 66 individuals with viral-bacterial pneumonia of a moderate severity associated

with COVID-19 (the main group). Their treatment included antibiotics, anticoagulants and intravenous injection of Lipin solution in the dose of 1000 mg per 100 ml of sodium chloride isotonic solution once a day during 7 days. The control group included 28 patients suffering from pneumonia who received antibiotics and anticoagulants only. In its turn, the main group included two subgroups: 1 – without comorbid type 2 diabetes mellitus (DM2) (34 patients); 2 – with comorbid DM2 (32 patients), who received additional nephroprotective and hypoglycemic therapy. Lipin was indicated in the dose of 35 mg/kg of the body weight once a day. The drug was introduced intravenously by drops slowly. The course of treatment lasted 7-10 days. Patients with diabetic nephropathy received Lipin in the dose of 10 -20 mg/kg of the body weight once a day in combination with the standard basic therapy. The drug was introduced intravenously by drops slowly. The course of treatment lasted 7-10 days.

The diagnosis of pneumonia was made according to the Adapted Clinical Recommendations based on the evidences «Community Acquired Pneumonia of Adults: Etiology, Pathogenesis, Classification, Diagnostics, Antimicrobial Therapy and Prevention» (2019). Common clinical examination was carried out of all the patients, and additionally the following parameters were determined: O_2 saturation, the content of D-dimer in the blood, creatinine and urea, arterial blood pressure, heart rate, body temperature at the same period of day.

The studies conducted were performed keeping to the Guidelines for Good Clinical Practice (GCP, 1996), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the World Medical Association (WMA) Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (1964-2000), and the order of the Ministry of Health of Ukraine №690 dated 23.09.2009, where a human being is an object of research. The study was approved by the Biomedical Ethics Committee of the Bukovinian State Medical University (experimental study; (Minutes No. 36 dated 17.11.2020) The article is recommended for publication by the Commission on Biomedical ethics in biomedical scientific research the Bukovinian State Medical University the protocol No. 8 dated 22 of October 2021. The state registration number is 0114U002471.

The data obtained were statistically processed by means of statistical programs ,,Excel5.0'' with the calculation of mean value and standard deviation. Student's test was used to detect difference probability between the groups. Difference between the groups were considered to be reliable with the significance level $p < 0,05$. Mann- Whitney criterion was used for nonparametric calculations.

The results of the research obtained were statistically processed in the following way. The primary data of patients' examination were recorded in the data base. The stages of further processing included their formalization, standardizing and statistical analysis.

The data were preliminary checked for normal distribution by means of Shapiro-Wilk test, according to which the hypothesis on normal distribution does not deviate (p=0,05); in such cases parametric methods of statistical analysis were used – Student criterion (checked according to Levene's and Fisher criteria).

Nonparametric statistical methods were applied in case of deviation of the hypothesis on normal samples: Mann–Whitney U test. The results were considered to be reliable ($p<0,05$), which is generally accepted in medical-biological studies. Kruskal–Wallis H test was applied to assess the differences between the samples by the level of the sign examined. The correlation analysis was carried out by means of Spearman's Rank correlation coefficient. The methods of statistical processing were performed on the personal computer applying the program for medical-biological studies Statistica 10, Microsoft Excel and «BioStat». The diagrams were drawn by means of the licensed copy of the computer program Excel (Microsoft Access-2000 (® Microsoft Corporation., 1992-1999)).

Results

On admission to the hospital the patients of all the groups were running temperature to 38°C and higher (80 % - 97 % of patients), weakness (40 % - 68 %), loss of appetite (from 40 % to 80 %), muscle pain (10 % - 30 %), cough (50 % - 85 %), positive PCR test on SARS CoV-2 antigen (89% of patients), excessive perspiration practically of all the patients, dyspnea

during exercise (31 % - 40 %), impaired taste and smell (25-40% of individuals) and reduced O_2 saturation within 88-93%. The signs of changes in the lungs detected by means of computed tomography of the chest typical for viral lesion of various degrees of severity from 10% to 50% of the lung surface were registered in 100% of patients.

Condition of patients after treatment improved in both groups, but in the main group it was faster than in the control one (4-5 faster): shortness of breath decreased, D-dimer in the blood reduced, high blood pressure and temperature came to normal values, O_2 saturation improved. Moreover, by the findings of chest X-ray carried out three weeks after treatment the patients from the main group presented faster decrease of infiltration areas in the lungs, and formation of stable fibrous changes respectively (See Table 1).

Pneumonias associated with COVID-19 are known to intensify activity of the blood clotting system, increase of D-dimer level, high parameters of which are associated with the risk of clot formation and death. According to D-dimer level all the patients were divided into 4 subgroups: within the ranges more than 500, 1000, 3000 and more than 3000 ng/ml.

The results of our research indicate that D-dimer level in patients from both groups before treatment was irregular elevated (Table 2). The number of patients before treatment was approximately equal in both subgroups. The biggest number of patients was in the subgroup with D-dimer level from 1000 to 3 000 ng/ml - 11(32,35%) of patients from the main group and 9 from the control group (32,14%), 20 patients altogether.

The smallest number of patients - 12 and 13 before treatment was in the subgroup with D-dimer parameters: under 500 ng/ml, and under 1000 ng/ml respectively (See Table 2).

After treatment with Lipin D-dimer level in the blood of patients in both groups decreased but it still remained high. Examining the number of patients in the subgroups certain increase in the number of patients in the subgroups 1 and 2 was found. Thus, I group included 25 individuals (before treatment – 13) and II group – 17 individuals (12 before treatment). Therefore, in the main group of patients who received Lipin therapy a reliable decrease of D-dimer parameter after treatment was registered in comparison with the control group of patients.

The number of patients with high D-dimer parameters – from 1000-3000 and more than 3000 ng/ml decreased considerably. Thus, there were 21 patients in I group before treatment, and after treatment there were only 9 individuals with high D-dimer in the group. At the same time, in II group there were 16 individuals before treatment and 11 after it. That is, D-dimer decreased 31,25% slower than in the patients from II group. High D-dimer in the patients from I group 57,15% decreased (See Table 3).

Discussion

The use of Lipin in a comprehensive treatment of patients suffering from pneumonia associated with COVID-19 demonstrates its potential possibility to reduce the level of D-dimer in the blood of patients.

According to the literary data phospholipids are known to slow down collagen synthesis and increase collagenase activity (enzyme destructing collagen). [16] Since collagen promotes replacement of the epithelial tissue by the connective one, phospholipids possess anti-fibrotic effect [17].

Patients with comorbid diabetes mellitus the course of the disease was more severe, since in addition to respiratory failure renal failure increased, which was accompanied by increasing of creatinine and urea level in the blood and decrease of glomerular filtration rate. To normalize the above parameters sorbents were added to therapy (Sorbex 2 tablets 3 times a day 30 minutes after meals, Corvitin 0,5g per 100 ml of physiological solution intravenous drops once a day, Canephron 2 tablets 3 times a day, ACE inhibitors and hypoglycemic therapy recommended by endocrinologists).

The results of the research showed that Lipin use produced a positive effect on the hemodynamic parameters, decreasing heart rate, normalizing arterial blood pressure[18]. Lipin administration results in decrease of general weakness, perspiration, increase of tolerance to physical exercises, leading to improvement of general condition and reduction of signs of respiratory failure [19]. Lipin produced a positive effect on reduction of D-dimer level in the blood of patients, decreasing the risk of clot formation and the risk of lethal outcome, normalizing kidney function in patients with comorbid pathology [20].

Lipin use did not provoke any side effects or allergic reactions. Sharp drop of BP was registered

in one case after rapid i/v injection, and the use of drug was discontinued.

Our own experience of Lipin administration confirms a protective action of the drug from the point of view of advanced irreversible fibrous changes in the lungs, especially in case of viral pneumonias associated with increased function of blood clotting.

The results of clinical studies confirm that Lipin-Biolik is an effective pathogenic therapeutic agent producing a positive effect on the pathophysiological chains with respiratory failure syndrome among patients of different ages

Thus, the results presented in the article confirm a high effect of Lipin (liposomal forms of natural phosphatidylcholine) for the treatment of viral pneumonias in practical work of a pulmonologist with the aim to reduce the risk of fibrosis formation in the lung tissue, the risk of clot formation and as surfactant-protective therapy.

References

1. Bezkaravainy BA, Kogutnitskaya MI Preparations of natural phosphatidylcholine: prospects for use in pediatrics // Child Health. - 2007. - № 6 (9). - P. 100-105.
2. Sirostan A. Lipin: restoring cells, wins the disease / A. Sirostan. - Pharmacy. - 2004. - № 45. - C.4.
3. Shinkarenko ND, Bezruk AI, Gedo AP, Mikhailenko AF, Zhivitsa EV. // Emergency medicine. - 2016. - №4 (75). - with. 24-27. The effectiveness of the use of lipin in the treatment of COPD with anemic syndrome in persons with pulmonary tuberculosis / MN Гришин, B.A. Лимарев, Ю.А. Зайцев, E.O. Korchagina // Crimean Therapeutic Journal. - 2014. - №1. - P. 102-104.
4. Yulish EI, Abaturov AE Liposomal therapy: present and future // Child health. - 2008. - № 1 (10). - P. 87-90.
5. Furse S., de Kroon AI. Phosphatidylcholine's functions beyond that of a membrane brick / S. Furse, AI. de Kroon // Mol Membr Biol. - 2015. – V. 32(4). – P.117-9.
6. Pawlak M., Lefebvre P., Staels B.J. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease / M. Pawlak, P. Lefebvre, B.J. Staels // Hepatol. – 2015. – V.62(3). – P. 720-733.
7. Adapted evidence-based clinical guideline "Nosocomial pneumonia in adults: etiology, pathogenesis, classification, diagnosis, antimicrobial therapy and prevention". Kyiv, 2019.
8. Order of the Ministry of Health of Ukraine dated 02.04.20. № 762 (as amended by the order of the Ministry of Health of Ukraine dated 21.07.20 № 1653 - Protocol for the provision of medical care for the treatment of coronavirus disease (COVID-19)).https://moz.gov.ua/article/ministry-mandates/nakaz-moz-ukraini-vid-21072020–1653-pro-vnesennja-zmin-do-protokolu–nadannja-medichnoi-dopomogi-dlja-likuvannja--koronavirusnoi-hvorobi-covid-19
9. Yi Y. Lagniton, Ye S., Li E., et al. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci. 2020; 16 (10): 1753–1766.
10. He F., Deng Y., Li W. Coronavirus disease 2019: What we know? J Med Virol. 2020; 10: 1002-23.
11. Kobelyatsky Yu.Yu. Features of the pathogenesis of coronavirus infection and promising areas of therapy. Medical newspaper "Health of Ukraine of the21st century" № 8 (477), April 2020 http://health-ua.com/article/60327-osobennosti-patogeneza-koronavirusnoj-infektcii-iperspektivnye-napravleniya
12. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 13 March 2020. World Health Organisation
13. Gurung A., Scrafford C.G., Tielsch J.M. et al. Computerized Lung Sound Analysis as diagnostic aid for the detection of abnormal lung sounds: a systematic review and meta-analysis. Respir Med. 2011; 105 (9): 1396–1403.
14. Hansen J.E., Sun X.G., Wasserman K. Spirometric criteria for airway obstruction: use percentage of FEV1/FVC ratio below the fifth percentile, not <70%. Chest. 2007; 131 (2): 349–355.
15. Xu Z., Shi L., Wang Y. et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8 (4): 420–422.

16. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; e201585.
17. Huang C., Wang Y., Li X. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395 (10223): 497–506.
18. Hanff T.C., Harhay M.O., Brown T.S. et al. Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System-a Call for Epidemiologic Investigations. Clin Infect Dis. 2020;ciaa329.
19. Thachil J., Tang N., Gando S. et al. Laboratory haemostasis monitoring in COVID-19. J Thromb Haemost. 2020 Apr 23.
20. Mehta P., McAuley D.F., Brown M. et al. COVID- 19: consider cytokine storm syndromes and immunosuppression. The Lancet Mar; S0140673620306280

Table 1. Parameters of arterial blood pressure, heart rate, content of urea, creatinine and D-dimer in the blood, oxygen saturation in patients with viral-bacterial pneumonias in dynamics of treatment (M±m)

Parameters	Main group before treatment (M±m) n=34	Control group before treatment (M±m) n=28	Main group after treatment (M±m) n=34	Control group after treatment (M±m) n=28
O_2 saturation	89,2±0,4	90,3±0,3	95,2±0,3	93,4±0,5
Systolic BP Hg	154,5±1,8	158,4±2,4	128,3±0,8	139,3±1,3
Creatinine mcmol/L	144,6±0,6	95±0,7	123,8±1,42	94,2±0,43
Urea mmol/L	10,4 ±1,78	7,2±1,23	9,1±0,89	6,68±1,1
Diastolic BP Hg	89,3±1,4	88,2±1,5	76,2±1,6	86,3±1,5
HR per 1 min.	110,4±2,5	112,4±3,3	78,2±4,3	91,2±3,7
Note: p=0,05				

Table 2. Parameters of D-dimer in patients with pneumonias before treatment

D-dimer (ng/ml)	I and II groups before treatment (M±m)	Number of patients I group (%)	Number of patients II group (%)
1 subgroup (D-dimer ≤500)	384,36±5,6	7 (20,53%)	6(21,42%)
2 subgroup (D-dimer ≤1000)	762,5±6,7	6 (17,65%)	6(21,42%)
3 subgroup (D-dimer ≤3000)	1790,27±7,4	11(32,35%)	9(32,14%)
4 subgroup (D-dimer ≥3000)	6050,00±13,6	10(29,41%)	7(25,0%)
Note: p=0,05			

Table 3. Parameters of D-dimer in patients with viral-bacterial pneumonias after treatment (M±m)

D-dimer ng/ml	I and II groups after treatment (M±m)	Number of patients I group (%)	Number of patients II group (%)
1 subgroup (D-dimer ≤500)	370,4±6,3	13(38,23%)	10(21,42%)
2 subgroup (D-dimer ≤1000)	793,11±12,5	12(35,29%)	7(25,0%)
3 subgroup (D-dimer ≤3000)	2896,78±14,5	5(14,70%)	7(25,0%)
4 subgroup (D-dimer ≥3000)	5980,23±11,4	4(11,76%)	4(14,28%)
Note: p=0,05			