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THE TREATMENT OF PATIENTS WITH ASTHMA AND COMORBIDITY

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Abstract. The treatment of patients with asthma and comorbidity. Yeryomenko G.V., Bezditko T.V. The increasing prevalence of asthma (A) and diabetes mellitus type 2 (DM2T) necessitates administration of the adequate antiasthmatic long-term basic therapy with consideration of comorbid states. The purpose consisted in revealing the therapeutic potential of Tiotropium bromide (TB) and L-arginine (Tivortine) in patients having uncontrolled moderately
severe asthma in combination with DM2T (A+DM2T). Forty seven A+DM2T patients underwent an in-depth study before and after their treatment. They were divided into 2 groups: treatment (group 1, n=28) and comparison (group 2, n=19). Both groups received the standard 2-component therapy: budesonide/formoterol fumarate dihydrate – 160/4.5 µg by 2 breaths twice a day and metformin at a dose of 500 mg twice a day. The complex of their basic therapy for group 1 additionally included TB (18 µg a day) and arginine hydrochloride preparation (Tivortine® aspartate, Yuraya-Farm) orally by 15 ml twice a day during 3 months (90 days). The patients were followed up 3 months and one year later. Their general condition demonstrated positive dynamics in both groups, the number of exacerbations in group 1 reducing by a factor of 4. The complex use of L-arginine and TB preparations against a background of the basic therapy in A+DM2T patients produced a better control over the disease, a more rapid elimination of obstruction manifestations, achievement and prolongation of the clinical spirometric remission, an improvement of the quality of life, correction of disturbances in haemocoagulation, fibrinolysis and the functional state of endothelium.

Treatment of comorbid states is one of important problems in medical practice. Ageing of population, bad habits, hypodynamia, irrational nutrition and a worsening ecological situation create conditions for a constant stress of the adaptive and biochemical mechanisms in the organism of the modern man with a resultant formation of several diseases in it. The prevalence of comorbid pathology in patients averages 78.6%, this condition occurring in 82% of cases in women and 72% in men [2]. The number of comorbid diseases in one patient considerably increases with age. For example, researchers have revealed that multimorbidity rises from 10% at the age, which does not exceed 19 years, to 80% in people at the age of 80 and older [14]. The simultaneous presence of several diseases affects each of them, aggravating their course, facilitating an earlier formation of complications and creating difficulties for therapy. The risk of death in case of two concomitant diseases is 5-10% and rises up to 70-80%, when their number increases up to five. Especially noteworthy is a combination of diseases, which have common or close aetiological and pathogenetic factors. The European standard of the GINA (2016 revision) for asthma contains a list of concomitant diseases, which can affect the course of the main pathology in a patient so much that the basic treatment is insufficient and becomes ineffective. Such diseases include rhinitis and rhinosinusitis, gastrointestinal reflux disease, night apnoea as well as diabetes mellitus and obesity [6, 19, 20].

It is possible to achieve the full or partial control of asthma (A) in the majority of patients under conditions of the correct assessment of its severity, the available level of asthma control and administration of the adequate antiasthmatic long-term basic therapy with consideration of comorbid states [21]. Pharmacotherapy is an essential component of treatment for any asthma. According to contemporary views on treatment of asthma, the main drugs for maintaining control over symptoms are provided by inhaled glucocorticosteroids (IGCS) with the personalized approach and attempts to separate single phenotypes of the disease with a subsequent development of the individual treatment plan (GINA, 2017) [15]. At present there is no need to prove advantages of combined therapy in fixed combinations of IGCS with long-acting β2agonists (LABA) over monotherapy with IGCS.

Active searches are constantly made for relationships between the phenotype, genotype, mechanisms of the disease development and appearance of
concomitant pathology, which may result from the therapy given. In future the above will make it possible to develop an algorithm for administering drugs depending upon the variant of the disease course [9, 20]. But it is believed that the most essential and clinically significant feature in the course of asthma in patients with diabetes mellitus type 2 (DM2T) consists in their overweight and obesity, thereby hindering the expected decrease of the disease severity in the process of treatment [19, 16]. Besides, the patients from this group demonstrate less efficiency of their basic therapy with use of IGCS; this fact often requires an increase in the daily dose of the used drugs with a resultant disturbance of carbohydrate metabolism [10, 13, 17]. In this connection it is necessary to study further the mechanisms of appearance of resistance to treatment and progression of asthma, combined with DM2T. The problem necessitates a multidimensional approach to diagnosis with inclusion of inflammatory markers, which are required for correction of the treatment.

Purpose – to reveal the therapeutic potential of Tiotropium bromide (TB) and L-arginine (Tivortine) in patients having uncontrolled moderately severe asthma in combination with DM2T (A+DM2T) on the basis of study of their influence on the functional state of lungs, the endothelial function and glucometabolic disturbances.

MATERIALS AND METHODS

The study involved 47 patients with A+DM2T before and after their treatment. The control group consisted of 20 apparently healthy people. The patients’ diagnosis and treatment were made in compliance with Order No. 868 of the Ministry of Health of Ukraine dated October 8, 2013 “On Approval and Implementation of Medical-Technological Documents on Standardization of Medical Aid in Asthma” [8]. The diagnosis and treatment of concomitant DM2T were made by a skilled professional in endocrinology according to effective Ukrainian protocols [7]. The patients were divided into two groups: the treatment group (group 1, n=28) and the comparison group (group 2, n=19). Both groups of patients received the standard 2-component therapy: budesonide/formoterol fumarate dehydrate – 160/4.5 µg (IGCS+LABA) in a dry powder inhaler by 2 breaths twice a day and metformin at a dose of 500 mg 2 times a day. Salbutamol sulphate in a metered dose inhaler (100 µg “on demand”) was used as an “emergency care” drug. The complex of their basic therapy for patients from group 1 additionally included TB (18 µg a day) and arginine hydrochloride preparation (Tivortine® aspartate, Yuriya-Farm) orally by 15 ml 2 times a day, the course of treatment lasted 3 months (90 days). The patients were followed up 3 months and one year later.

The patients’ personal data included their gender, age, weight, body mass index (BMI) and history of exacerbations. On day 1 as well as after 3 and 12 months since the beginning of therapy the following examinations were made: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), forced expiratory volume (FEV1), Tiffeneau-Pinelli index (FEV1/FVC), forced expiratory flow on the levels of 25, 50 and 75% (FEF25, FEF50, FEF75), as well as such general clinical and biochemical indices as glycated haemoglobin (HbA1c,%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (A+DM2T)</th>
<th>Group 2 (DM2T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycated Haemoglobin (HbA1c, %)</td>
<td>9.0 (8.0-10.0)</td>
<td>6.5 (5.5-7.0)</td>
</tr>
<tr>
<td>Fasting Blood Glucose Level (r)</td>
<td>110 (100-120)</td>
<td>80 (70-90)</td>
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<tr>
<td>FEV1/FVC</td>
<td>0.75 (0.70-0.80)</td>
<td>0.80 (0.75-0.85)</td>
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<tr>
<td>FEF25/FVC</td>
<td>0.75 (0.70-0.80)</td>
<td>0.80 (0.75-0.85)</td>
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<tr>
<td>FEF50/FVC</td>
<td>0.75 (0.70-0.80)</td>
<td>0.80 (0.75-0.85)</td>
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<tr>
<td>FEF75/FVC</td>
<td>0.75 (0.70-0.80)</td>
<td>0.80 (0.75-0.85)</td>
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<thead>
<tr>
<th>Variable</th>
<th>Group 1 (A+DM2T)</th>
<th>Group 2 (DM2T)</th>
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</thead>
<tbody>
<tr>
<td>FEV1 (l)</td>
<td>2.5 (2.3-2.7)</td>
<td>3.0 (2.8-3.2)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>3.0 (2.8-3.2)</td>
<td>3.5 (3.3-3.7)</td>
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<tr>
<td>FEF25 (l/s)</td>
<td>120 (110-130)</td>
<td>150 (140-160)</td>
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<tr>
<td>FEF50 (l/s)</td>
<td>180 (170-190)</td>
<td>220 (210-230)</td>
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<tr>
<td>FEF75 (l/s)</td>
<td>240 (230-250)</td>
<td>300 (290-310)</td>
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The content of monocyte chemoattractant protein-1 (MCP-1) and matrix metalloproteinase-9 (MMP-9) in blood serum was determined by the method of enzyme immunoassay (ELISA) with help of “HUMAN MCP-1” and “HUMAN MMP-9” kits (eBioscience, Austria), von Willebrand factor (VWF) by the photometric method modified by Koval’ova O.M. [4]. The state of external respiration (ER) was assessed on the basis of the forced respiration curve, which was registered on a SpiroCom spirograph (Ukraine). The following parameters were assessed: FVC, FEV1, FEF25, FEF50, FEF75. The assessment of the severity of asthma attacks and the level of the disease control was formalized and made according to the Asthma Control Questionnaire (ACQ) [11] and Asthma Quality of Life Questionnaire (AQLQ) [8]. The study findings were statistically processed with use of SPSS 19 program for Windows (IBM, USA). Quantitative variables were described by the following parameters: the median (Me) and the 25th and 75th percentiles (Me[25%-75%]). In order to reveal differences between independent samples, the Mann-Whitney U test was used. The normality of data distribution was analysed with help of the Shapiro-Wilk test.

RESULTS AND DISCUSSION

Analysis of the findings revealed that after 12 months of the regular taking of the IGCS/LABA combination most of the ER indices in the examined groups tended to improve. But for the majority of characteristics these changes were not statistically significant (Fig. 1). Values of inflammatory markers in patients from group 1 decreased: MCP-1 from 806.14 ng/ml to 534.50 ng/ml (p=0.047), MMP-9 from 768.5 ng/ml to 576.50 ng/ml (p=0.032), IL-1β from 136.14 ng/ml to 93.31 ng/ml (p=0.003), TNF-α from 430.71 ng/ml to 243.26 ng/ml (p=0.001), IL-6 from 631.70 ng/ml to 430.25 ng/ml (p=0.002), IL-8 from 806.14 ng/ml to 534.50 ng/ml (p=0.013), MMP-9 from 788.5 ng/ml to 534.50 ng/ml (p=0.002).
The above was accompanied with an improvement of the endothelial function: a reduction of VWF (Fig. 2) and an elevation of S-NO (Fig. 3). At the same time, there were no reliable changes of these indices in patients from group 2 (Figs. 4 and 5). Such a reduction of VWF as a decrease of the vasospatstic state of endothelium under the effect of Tivortine and TB was revealed. At the same time, especially noteworthy is an increased content of nitric oxide metabolites (S-nitrosothiols) as indicators of functioning of vasodilatory mechanisms of cellular interactions. The latter fact can be regarded as the compensatory intensification of vasodilatory activity in response to a reduced action of VWF.

Results of analysis of carbohydrate metabolism reliably demonstrated decreases of HbA1c% (from 7.50 [7.07-7.90]% to 6.3[5.95-6.72]%, p=0.01) and the glycaemic load level (from 6.90 [6.02-7.40] mmol/l to 6.01[5.20-6.61] mmol/l, p=0.03) in patients from group 1 and absence of reliable changes in group 2.

The number of A+DM2T exacerbations during 12 months of follow-up was calculated on the basis of personal encounters of the patients and data of analysis of medical documents. Under the influence of the chosen treatment the number of exacerbations in group 1 decreased by a factor of 4 (down to [1.0-2.0] cases a year), and these changes were reliable (p=0.001). In group 2, on the contrary, this index improved but remained unreliable, it causing involvement into the study from 4.0 [4.0-5.0] cases a year to 3.0 [2.5-4.5] cases a year (p=0.607). The quality of life in patients from groups 1 and 2 improved (respectively, the general quality of life by 46% and 29%, the physical component of health by 34% and 18%, the mental component of health by 46% and 21%), the degree of asthma control increasing in patients from group 1 by 21% and in patients from group 2 by 12% by ACQ data. Analysis of anthropometric data changes showed a decrease of BMI in group 1 from 28.5 [26.7-32.5] kg/m² to 27.01 [24.59-30.3] kg/m², (p=0.001).

The findings clearly demonstrate that it is reasonable to administer the combination of L-arginine and TB against a background of the basic therapy to patients with A+DM2T for reducing a possibility of exacerbations and improving the prognosis for the course of the disease [12, 18, 21].

It is known that the use of Tivortine in treatment of patients produces an effect on the endothelial function and improves its state, catalyzes the synthesis of nitric oxide in endotheliocytes, increases the level of cyclic guanosine monophosphate (cGMP) in vascular endothelium, decreases activation and adhesion of leukocytes and thrombocytes to vascular endothelium and inhibits the synthesis of MCP-1 [3, 5, 6].
Fig. 2. The dynamics of changes in VWF under the effect of treatment (%)
Fig. 3. The dynamics of changes in S-NO under the effect of treatment (μmol/l)
Fig. 4. The dynamics of the number of complications per year under the effect of treatment
Fig. 5. The dynamics of ACQ under the effect of treatment
CONCLUSIONS
1. The complex use of L-arginine and TB preparations against a background of the basic therapy in patients with asthma combined with DM2T resulted in correction of disturbances in haemocoagulation, fibrinolysis and the functional state of endothelium with a better control over the disease.
2. When treating patients with asthma combined with DM2T it is reasonable to include L-arginine and TB preparations into the complex therapy due to the positive effect on the patients’ general condition, a more rapid elimination of obstruction manifestations, achievement and prolongation of the clinical spirometric remission, and an improvement of the quality of life.
3. Comparison of the patients’ indices from groups 1 and 2 before the treatment, after 3 months and after 1 year.

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