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The efficacy of decamethoxine as a part of multimodality therapy of infectious exacerbations of bronchial asthma

Key words: *bronchial asthma, decamethoxine, infectious exacerbation.*

In the recent years, there has been a consistent growth of the incidence of bronchial asthma (BA) in majority of countries worldwide. According to literature, from 1.0 % to 10.0 % of global population have BA. On the average, BA affects approximately 5.0 % to 7.0 % of the population [8]. According to official statistical data, the 2011 incidence of asthma in Ukraine was 515.9 patients per 100,000 of adult population; with each year, this number is steadily increasing [7].

Exacerbations of asthma (especially severe ones) cause deterioration of pulmonary function (which persists for prolonged periods of time and frequently fails to return to baseline); this aggravates both the course and prognosis of the disease [9, 11].

It has been proved that viral respiratory infections are a leading cause of BA exacerbations [12]. One of the components of the adverse impact of viral respiratory infection is creating the preconditions for bacterial superinfection and formation of viral-bacterial associations [10]. Therefore, the results of treatment of acute BA exacerbations greatly depend on adequate antibacterial therapy. However, there is currently no consensus concerning the strategy of antibacterial treatment and its administration routes.

In recent years, there are reports concerning the efficacy of decamethoxine-based antiseptic agents in the therapy of purulent and destructive pulmonary conditions, pneumonia and infectious exacerbations of chronic obstructive pulmonary disease [1, 2, 4]. A number of in vitro studies have demonstrated high sensitivity of viral and bacterial agents of infectious exacerbations of bronchial asthma to decamethoxine [5, 6]; it was also demonstrated that inhalations of 0.02 % solution of decamethoxine do not exert any negative influence on parameters of respiratory function (RF) in patients with infectious exacerbations of BA [3]. However, the efficacy of nebulised antimicrobial therapy with decamethoxine in patients with infectious exacerbations of BA has not been studied sufficiently, which has led the investigators to the **aim of the study:** to investigate clinical efficacy and substantiate the expedience of adding 0.02 % solution of decamethoxine (administered as inhalations) to the multimodality therapy of infectious exacerbations of bronchial asthma.

Materials and methods of the study

To meet the objectives of the study, we have selected 64 patients with virus-induced BA exacerbations, which were treated at the Department of therapeutic technologies in non-specific lung disease of the State Institution 'The National Institute for Tuberculosis and Pulmonology named after F. G. Yanoskyi of the National Academy of Medical Sciences of Ukraine' in 2012-2014. The diagnosis of infectious exacerbation of BA was established according to the guidelines specified in the Order of the Ministry of Health of Ukraine 'Concerning the approval and implementation of medical and technological documents for standardization of care in bronchial asthma' No. 868, dated 08.10.2013. [7].

The patients which did not receive adequate therapy for their BA exacerbations had their treatment adjusted accordingly. Depending on the severity of the exacerbation, the patients received anti-inflammatory drugs (inhaled and/or systemic steroids) in combination with bronchodilators (2-agonists and anti-cholinergic drugs of short and prolonged action). The scope of therapeutic interventions and routes of administration of the drugs (inhaled, oral or parenteral) were determined depending on the severity of the exacerbation and on the response to the initial stage of therapy according to the recommendations in the Order of the MoH of Ukraine No.868 dated 08.10.2013. [7]. Mucolytic agents and antihistamines were simultaneously used when indicated.

It should be noted that all patients with BA received their basic therapy according to the severity of their disease and per

current standards of treatment; the therapy was conducted for at least 4 weeks before the occurrence of a virus-induced BA exacerbation and enrolment of patients to the study.

When making the diagnosis of virus-induced BA exacerbation, the following factors were taken into account: history of the disease, clinical symptoms of BA exacerbation, Asthma Control Test and symptoms of toxic syndrome, parameters of respiratory function (spirometry and peak expiratory flow, PEF) and the reversibility of bronchial obstruction in a bronchodilator test.

All 64 patients with virus-induced BA exacerbation, enrolled to an open-label randomised study, were distributed into two groups.

The main group (Group 1): 41 patients (17 males and 24 females); mean age 48.2 ± 11.7 years, FEV1 = 66.8 ± 2.4 %, the increment in a bronchodilator test: 15.7 ± 2.0 %. As a part of multimodality therapy, these patients received 0.02 % solution of decamethoxine, 4 mL via inhalation (through a nebulizer) twice a day for 10 days.

The control group (Group 2): 23 patients (9 males and 14 females); mean age 47.4 ± 13.9 years, FEV1 = 64.9 ± 2.7 %, the increment in a bronchodilator test: 16.4 ± 2.8 %; these patients received standard therapy only (matching the severity of BA exacerbation).

According to the findings of clinical and instrumental assessment, patients with moderate BA exacerbations

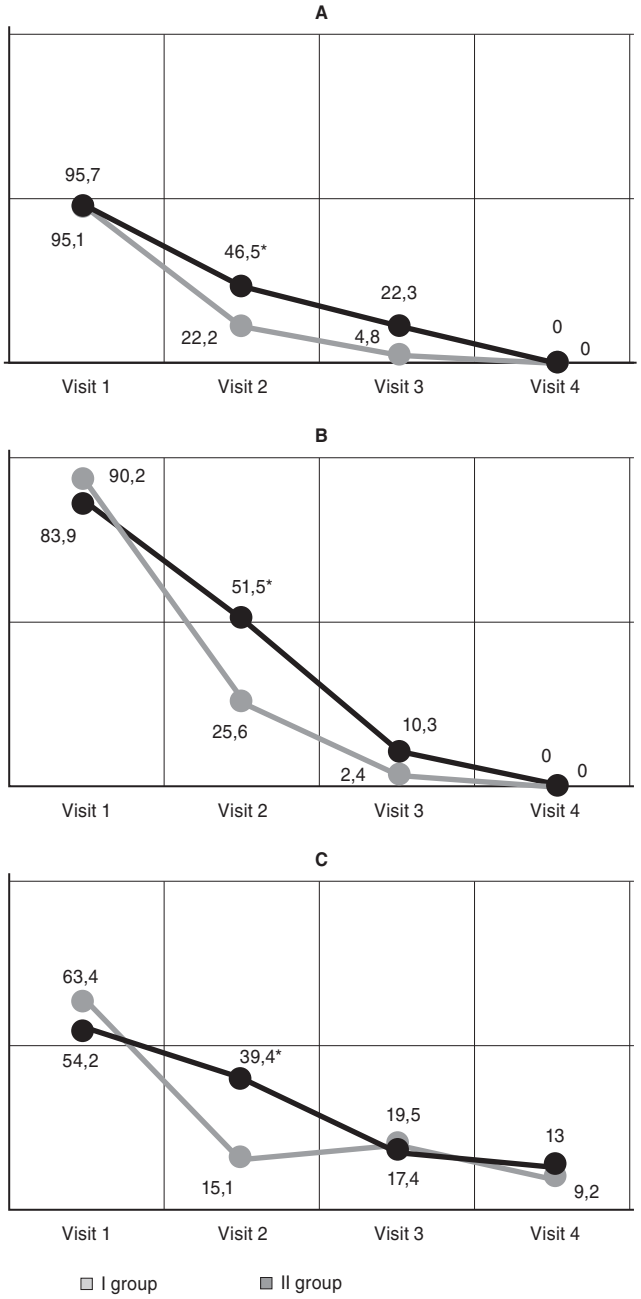

Fig. 1**. **The trends concerning the main clinical manifestations of toxic syndrome.**

* The difference of parameters compared to Group 1 is statistically significant (p < 0.05).
** [Please note: In the figure above, comma is used as a decimal separator]

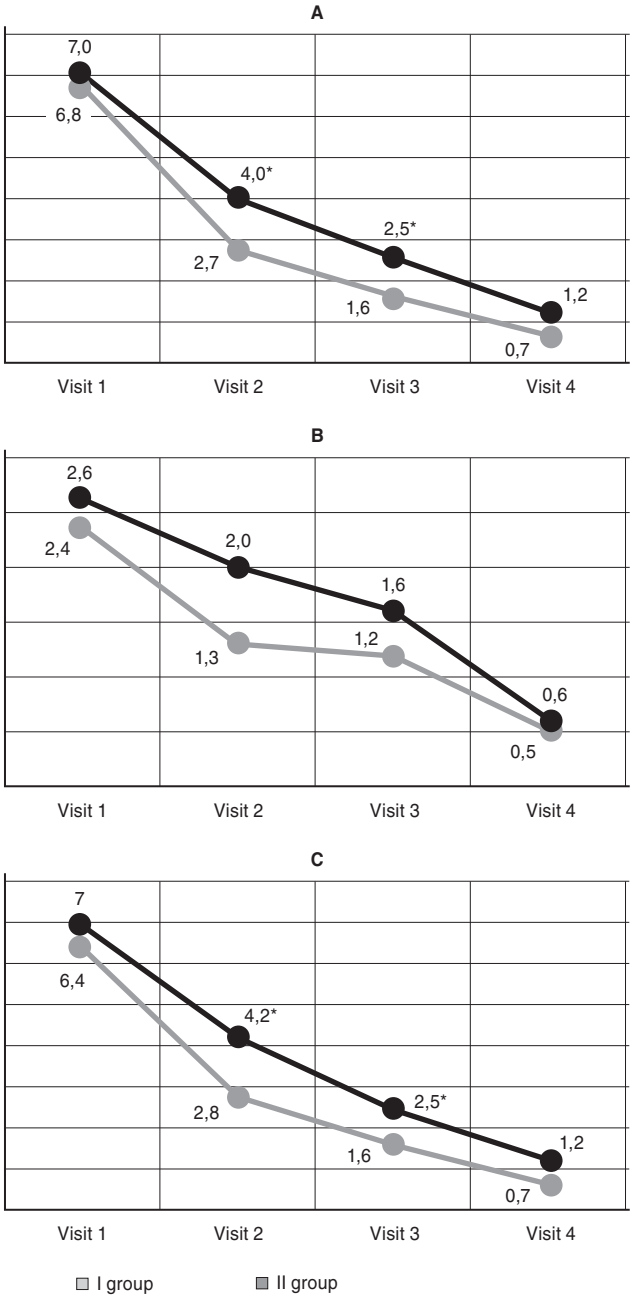

Fig. 2**. **Changes of clinical symptoms with time (virus-induced BA exacerbation)**

* The difference of parameters compared to Group 1 is statistically significant (p < 0.05).
** [Please note: In the figure above, comma is used as a decimal separator]

Table

The changes of RF in patients of study groups (M ± m)

Parameters	Visit 1		Visit 2		Visit 3	
	Main (n = 41)	Control (n=23)	Main (n = 41)	Control (n=23)	Main (n = 41)	Control (n=23)
FEV_1, % of normal	66,8 ± 2,4	64,9 ± 2,7	74,6 ± 2,6#	76,4 ± 2,2#	81,6 ± 2,5#	77,9 ± 2,3#
Morning PEF, L/min	236,6 ± 13,2	230,9 ± 14,5	254,0 ± 14,1	249,0 ± 15,3	302,7 ± 13,8#	293,5 ± 15,1#
Evening PEF, L/min	265,4 ± 14,9	266,4 ± 15,4	268,6 ± 16,8	270,6 ± 13,8	289,3 ± 13,6	290 ± 15,1
Daily PEF variability, %	32,9 ± 4,9	33,1 ± 2,7	26,1 ± 2,0	27,6 ± 2,4	18,0 ± 1,8	20,3 ± 2,0
The increment in a bronchodilator test, %	15,7 ± 2,0	16,4 ± 2,8	13,5 ± 2,4	14,1 ± 2,6	10, 2 ± 1,8#	11,5 ± 2,7

Note. # The difference of parameters in the group (compared to Visit 1) is statistically significant ($p < 0.05$).

dominated both in the main and in the control group (81.3 ± 4.9 % of all patients).

At the start of study enrolment, the patents filled out the Asthma Control Test questionnaire. The results of this test have demonstrated that most patients in the main group and in the control group had uncontrolled disease: 13.4 ± 0.4 and 13.7 ± 0.5 points, respectively.

In terms of main signs (the severity of virus-induced BA exacerbation, age, anthropometric measures and concomitant disease), there were no differences between the patients of Group 1 and Group 2 ($p > 0.05$).

The patients had a complete examination at the start of study enrolment, when group-appropriate therapy schedules were assigned: Visit 1, Visit 2 (at Day 3 of treatment), Visit 3 (at Day 7 – Day 10 of treatment) and Visit 4 (at Day 18 – Day 20 from the onset of observation).

Efficacy assessment of a 10-day course of inhaled 0.02 % solution of decamethoxine as a part of multi-modality therapy of BA exacerbation was performed judging by the temporal changes in toxic syndrome, clinical symptoms of BA, RF parameters, PEF and the fraction (%) of patients that required systemic antibiotic therapy during or after the treatment.

The results were processed and analysed using the methodology of analysis of variance. Student's t-test was used to compare the populations which followed normal distribution. When the population could not be assumed to be normally distributed, non-parametric analogues of Student's t-test were used: Wilcoxon signed-rank test and Wilcoxon rank-sum test for linked samples and independent samples, respectively. The null hypothesis of the absence of significant differences between the matched populations was rejected at p value 0.05. The study was financially supported by the State Budget.

Results

Appending the therapy of a BA exacerbation with 0.02 % solution of decamethoxine had a positive influence on the course of virus-induced exacerbations of BA. Thus, the positive trends concerning the main clinical manifestations of toxic syndrome were documented already Day 3 of treatment (Visit 2) in both groups (see Fig. 1).

However, in patients of Group 1 the investigational parameters were changing significantly rapidly than in the control group. Low-grade fever persisted only in (22.2 ± 7.0 % patients of Group 1 and in 46.5 ± 10.6 % patients of Group 2 ($p < 0.05$), profuse sweating was found in 25.6 ± 7.6 % patients of Group 1 and in 51.5 ± 10.6 % patients of Group 2 ($p < 0.05$); headache was found in 15.1 ± 5.9 % patients of Group 1 and in 39.4 ± 9.8 % patients of Group 2 ($p < 0.05$).

In the following stages of study, there were consistently more dynamic positive trends of the main clinical manifestations of toxic syndrome in Group 1, which contributed to a faster (by an average of 1-2 days) resolution of the main clinical manifestations of toxic syndrome.

The analysis of clinical symptoms of virus-induced BA exacerbation has demonstrated positive trends already at Day 3 of therapy in both groups (see Fig. 2).

In patients of the main group the aforementioned changes were faster in a statistically significant fashion than in the control group. Thus, there were on the average 2.7 ± 0.3 day-time BA episodes in the main group and 4.0 ± 0.2 episodes per day ($p < 0.05$) in the control group. The PRN bronchodilator use was 2.8 ± 0.5 doses/day in Group 1 and 4.2 ± 0.3 doses/day in Group 2 ($p < 0.05$). At the subsequent stages of treatment, the patients of the main group also had faster treatment responses.

At Treatment Day 4-5, 3 (7.3 ± 4.1 %) patients of the main group and 7 (30.4 ± 9.6 %) patients of the control group still had low-grade fever (above 37°C), which either persisted for more than 3 days from the onset of symptoms of respiratory viral infection or emerged after a previous recovery of normal body temperature. Fever was accompanied by more intensive cough and an increased secretion of mucus, which gradually became muco-purulent or purulent. The above symptoms indicated bacterial superinfection and required additional systemic antibacterial therapy. Taking into account that the non-specific inflammation developed in an in-patient setting, the patients received intravenous Levofloxacin 500 mg twice a day for 5 –7 days. The rate of bacterial complications in the control group was 23.1 % higher than in the main group.

The positive trends concerning clinical symptoms at all visits were confirmed by RF and PEV (see Table below)

There was a substantial improvement of RF at Treatment Day 3 (Visit 2) in both groups. Compared with the start of treatment, there was an increase of FEV1 from

66.8 ± 2.4 % to 74.6 ± 2.6 % in the main group ($p < 0.05$); the increase in a bronchodilator test reduced to 13.5 ± 2.4 %. In the control group there was an increase of FEV1 from 64.9 ± 2.7 % to 76.4 ± 2.2 % ($p < 0.05$); the increase in a bronchodilator test reduced to 14.1 ± 2.6 %.

Compared with Visit 1, there was a significant increase of FEV1 in the main group at Treatment Day 7 –10 (Visit 3), from 66.8 ± 2.4 % to 81.6 ± 2.5 %, $p < 0.05$; the increase in a bronchodilator test reduced to 10.2 ± 1.8 %, $p < 0.05$. There also was an increase of FEV1 from 64.9 ± 2.7 % to 77.9 ± 2.3 % in the control group ($p < 0.05$); the increase in a bronchodilator test reduced to 11.5 ± 2.7 %. When Group 1 and Group 2 were compared, FEV1 values tended to be higher in Group 1: 81.6 ± 2.5 % and 77.9 ± 2.3 % in Group 1 and Group 2, respectively.

Therefore, compared to standard inhaled therapy alone, complementing the therapy of infectious exacerbation of BA (according to current standards of treatment) with inhaled antiseptic solution of decamethoxine contributed to a faster elimination of toxicity and clinical symptoms of BA exacerbations and improved RF and PEV more significantly.

Conclusions

Using a 10-day course of inhaled 0.02 % solution of decamethoxine as a part of multi-modality therapy in patients with BA exacerbations ensures the control of the disease is achieved in 92.4 % patients.

Using a 10-day course of inhaled 0.02 % solution of decamethoxine (as a part of multi-modality therapy in infectious exacerbations of BA) is 23.1 % more effective than standard inhaled therapy.

Infectious exacerbation of BA is an indication to use a 10-day course of inhaled 0.02 % solution of decamethoxine.

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