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CLINICAL RESEARCH

The Effect of L-Arginine on the Clinical and Immunological Parameters in Patients with Asthma

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Abstract

The purpose of this study was to study the effects of L-arginine on the clinical course and some immunological parameters in patients with asthma. ***Material and Methods:*** In this study, we examined 56 patients with moderate and severe persistent asthma. The average duration of the disease was 15±2. 3 years. The patients were divided into two groups. The patients of the study group (n=25) were subjected to the standard treatment and nitric oxide (NO) donor L-arginine. The patients of the comparison group (n=31) received the standard treatment only. All patients underwent a complete physical examination including a determination of serum cytokine levels (IL-4, IL-8, and TNF-α) before and after treatment. ***Results:*** In both groups, the baseline serum levels of IL-4, IL-8 and TNF-Fα were greater than the normative values. Direct correlations were observed between the level of the interleukins and clinical symptoms. Daily intravenous infusion of L-arginine at 4.2 g for 30 min over 10 days significantly reduced the serum levels of IL-4, IL-8 and TNF-α. No significant changes were noted in the levels of these parameters in the control group. ***Conclusion****:* The addition of L-arginine to the basic treatment in asthmatic patients contributed to the earlier improvement of clinical symptoms and a significant reduction of the IL-4, IL-8 and TNF-α serum levels.

Key words*: asthma, L-arginin, interleukins, endothelial dysfunction.*

Introduction

Asthma is a serious public health problem, occurring across the world, affecting people of all ages. Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes [1-3]. Cytokines orchestrate the inflammatory response in asthma and determine its severity [4]. The nitric oxide (NO) has also been identified as a key mediator of asthma [1]. NO has been well described in the literature as an important signaling molecule involved in regulation of many mammalian physiologic and pathophysiologic processes, particularly in the lung. NO plays a role in regulation of both pulmonary vascular tone as well as airway bronchomotor tone through effects on relaxation of smooth muscle. In addition, NO participates in inflammation and host defense against infection via alterations in vascular permeability, changes in epithelial barrier function and repair, cytotoxicity, upregulation of ciliary motility, altered mucus secretion, and inflammatory cell infiltration [5,6].

Many studies show that asthma is associated with endothelial dysfunction in the conducting airway that is invested by the systemic circulation, and that inhaled glucocorticosteroids restore endothelial function in these conditions. Endothelial dysfunction presumably is an expression of airway vascular inflammation [7]. Endothelial dysfunction, expressed during

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the early stages of the disease, exacerbates respiratory failure, hypoxemia and tissue hypoxia, as well as promotes systemic and pulmonary hemodynamic disorders [8].

The goal of asthma management strategy is to achieve and maintain clinical control. To treat asthma there are two classes of medications: controllers (inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting inhaled β_2–agonists in combination with inhaled glucocorticosteroids, sustained-release theophylline, cromones, and anti-IgE) and relievers (rapid-acting inhaled β_2–agonists, inhaled anticholinergics, short-acting theophylline, and short-acting oral β_2–agonists). Despite significant progress in the control of asthma, many problems of the drug therapy are not fully resolved.

Since the identification of nitric oxide as a bioactive molecule involved in the pathogenesis of pulmonary disorders, many researchers have focused on the importance of the nitric oxide synthase (NOS) pathway involving conversion of L-arginine to NO and L-citrulline. L-arginine is produced from L-citrulline by cytosolic enzymes argininosuccinate synthetase 1 (ASS1) and argininosuccinate lyase (ASL). As the only substrate for NOS, L-arginine bioavailability plays a key role in determining NO production [5].

The purpose of this study was to study the effects of L-arginine on the clinical course and some immunological parameters in patients with asthma.

Materials and Methods

We examined 56 patients aged from 18 to 55 years (mean age 38.5±4.2 years) with the moderate and severe persistent asthma. The patients were staged according to GINA [1]. The average duration of the disease was 15±2.3 years. The patients were divided into two groups. After giving informed consent, the patients were divided into two groups. The patients of the study group (n=25) were subjected to the standard treatment and nitric oxide (NO) donor L-arginine. The patients of the comparison group (n=31) received the standard treatment only. The study was approved earlier by the Institutional Ethics Committee.

L-arginine (Tivortin, URiA-PHARM, Ukraine) was administered daily by intravenous infusion at 4.2 g for 30 min over 10 days. All patients underwent a complete physical examination including a determination of serum cytokine levels (IL-4, IL-8, and TNF-α) before and after treatment.

To assess the clinical efficacy, the Asthma Control Criteria including daytime symptoms, activity limitation, nighttime symptoms, and the need for emergency preparations were employed [1]. Symptoms were assessed on a five-point system to test for severity.

Serum cytokine levels were determined by ELISA. Commercial kits for IL-4, IL-8 and IFN-α measurement were purchased from Vector-Best (Novosibirsk, Russia).

Results were statistically processed using the computer software package Microsoft Excel (“Packet Analysis”). Quantitative parameters are presented as mean±SD. Analysis of the distribution of values obtained was performed using the Kolmogorov-Smirnov test. For data with normal distribution, inter-group comparisons were performed using Student's t-test. A value of $P<0.05$ was considered statistically significant.

Results

In both groups, baseline serum levels of IL-4, IL-8 and TNF-α were greater than the normative values. L-arginine addition to the basic treatment in patients with asthma contributed to the earlier improvement of clinical symptoms. Significant improvement of the clinical symptoms in the study group patients was recorded on the 3 - 4th day of treatment ($p<0.01$), whereas in the control group, the positive trend was recorded only on the 7 – 8th day and was not considered significant (Table 1).

Table 1.
The dynamics of clinical symptoms during treatment

Symptoms	Study group (n= 25)		Comparison group (n=31)	
	before	after	before	after
Daytime symptoms	4	1*	4	3*,**
limitation of activities	3	-*	4	3*,**
Nocturnal symptoms	5	1*	5	4*,**
Need for reliever/rescue treatment	4	-*	4	2*,**

***Note**: *- $p < 0.05$ with initial data; **- $p < 0.01$ between groups.*

The addition of L-arginine to the basic treatment significantly reduced the serum levels of IL-4, IL-8 and TNF-α on the 10th day treatment ($p<0.05$). No significant changes were noted in the levels of these parameters in the control group. Direct correlations were observed between the levels of the interleukins and clinical symptoms. The addition of L-arginine to the basic treatment in asthmatic patients contributed to the earlier improvement of clinical symptoms and a significant reduction of the IL-4, IL-8 and TNF-α serum levels (Table 2).

Table 2.
The dynamics of immunological parameters during treatment

Parameters	Study group (n= 25)		Comparison group (n=31)	
	before	after	before	after
IL-4 (0–20 pg/mL)	68.3±1.2	34.7±0.4*	66.7±1.5	54.2±2.3*,**
IL-8 (0–10 pg/mL)	34.3±1.6	18.2±0.8*	34.2±1.1	25.4±2.1*,**
TNF-α (0–6 pg/mL)	18.1±1.4	11.3±0.2*	18.5±1.2	15.2±1.9*,**

***Note**: *- $p < 0.05$ with initial data; **- $p < 0.01$ between groups.*

Conclusion

Thus, this study showed that the addition of Tivortin to the basic treatment in patients suffering from moderate and severe persistent asthma contributed to the earlier improvement of the clinical symptoms, particularly showing significant reduction in the IL-4, IL-8 and TNF-α serum levels. The preliminary positive results warrant further study of the possible effectiveness of L-arginine in patients with asthma.

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