



LEVOCETIRIZINE AND DESLORATADINE HAVE INFLUENCE ON PRO-INFLAMMATORY CYTOKINES' PLASMATIC LEVEL IN PATIENTS WITH PERSISTENT ALLERGIC RHINITIS.

Bocșan Corina Ioana¹, Bujor Adriana², Miron N.², Negulescu V.³, Cristea V.²

¹ Department of Clinical Pharmacology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania

² Department of Immunology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania

³ Department of Clinical Pharmacology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract. Allergic rhinitis is a chronic inflammatory disease which involves different cells and mediators. H1 antihistamines represent first line treatment in patients with allergic rhinitis. We evaluated the effect of H1 antihistamines on symptoms and pro-inflammatory cytokines plasmatic level in patients with persistent allergic rhinitis, after 4 weeks treatment, during continuous exposure to allergens.

79 patients, mean age 30.44±9.90 years, diagnosed with persistent allergic rhinitis were included in the study, divided into 2 groups: 39 patients were under treatment with Desloratadine 5 mg/day and 40 patients received Levocetirizine 5 mg/day for 4 weeks. The patients were evaluated before and after the treatment. We observed the rhinitis symptoms (sneezing, rhinorrhea, nasal congestion, nasal and ocular itching), total symptoms score, type of sensitisation (indoor or outdoor allergens), plasmatic levels of IL-6 and IL-8.

H1 antihistamines reduce total symptoms score, especially nasal congestion in patients with allergic rhinitis. IL-6 and IL-8 have no different plasmatic levels in patients with allergic rhinitis compared with the values obtained in healthy volunteers. Levocetirizine reduces the plasmatic level of both IL-6 and IL-8 after 4 weeks of treatment, while Desloratadine has influence only on the IL-6 level.

Keywords: allergic inflammation, pro-inflammatory cytokines, Levocetirizine, Desloratadine

Introduction

Allergic rhinitis is a nasal mucosa chronic disease, which affects 10-20% of general population, with an increasing prevalence [1]. This was observed especially in developing countries, like Romania; the prevalence rate is decreasing in western countries with previously high prevalence [1,2]. In phase III ISAAC study, an increasing rate of allergic rhinitis in 6-7 years age group was observed in most of the countries [2].

Allergic rhinitis is an IgE mediated disease, clinically characterized by sneezing, rhinorrhea, nasal congestion, nasal and ocular itching. It is due to a Th2 inflammatory response secondary to allergens

exposure, in which the cytokines and adhesion molecules play a key role. It was noticed that in patients with persistent allergic rhinitis Th2 cytokines' levels, like IL-4, IL-5 and IL-13 are increased compared with normal subjects [3]. On the other hand continuous exposure to allergens produces a chronic allergic inflammation. The eosinophil is the major cell involved in the late phase of the allergic response. It releases different types of cytokines involved in persistence of the inflammation (IL-1, IL-3, IL-5, IL-6, IL-8, TNF- α , TGF- α and β) [4,5].

IL-6 is a multifunctional cytokine, with both pro- and anti-inflammatory role. IL-6 production is induced by IL-1, IL-2 and TNF- α and it is inhibited by IL-4 and IL-13 [4]. IL-6 is a neutrophil activator, but in the same time inhibits the production of IL-1 and TNF- α and induced the synthesis of IL-1Ra [4,5]. Unlike IL-1, IL-6 does not induce the expression of ICAM-1 on the endothelial cells and this could balance the pro-inflammatory effect of IL-6 [6].

Bocșan Ioana Corina

Department of Clinical Pharmacology
Pasteur str, no.6, 400349, Cluj Napoca
Email: bocsan.corina@umfcluj.ro

Like IL-6, IL-8 has essentially a pro-inflammatory role and is one of the powerful chemoattractants for neutrophils. During inflammatory processes IL-8 is involved in a late phase compared with other chemoattractant mediators [4,5]. Both IL-6 and IL-8 present increased levels in nasal secretion in patients with allergic rhinitis after allergens specific nasal challenge tests [7,8,9]. IL-8 is increased especially in the late phase, 8 hours after exposure. But in normal exposure to allergens the IL-8 level is not different compared with healthy volunteers [10]. There is no data regarding the plasmatic level of the cytokines in patients with allergic rhinitis. It is well known that allergic inflammation is a systemic process and allergic rhinitis is a risk factor for asthma development. Approximately 30% of the patients with allergic rhinitis present asthma after a period of time [11].

H1 antihistamines are the largest class of medications used in allergic rhinitis and the first line treatment in all forms of the disease, in monotherapy or in association with other drugs [1]. Antihistamines have efficacy especially in controlling rhinorrhea, sneezing, nasal itching. But the newest compounds are efficient also in controlling the nasal congestion [12], probably due to an additional anti-inflammatory effect [13].

Levocetirizine is a potent antihistamine, the active R enantiomer of cetirizine. It has two fold affinity for H1 receptors compared to cetirizine and a lower one compared with desloratadine [14]. Several studies revealed that Levocetirizine could improve nasal congestion in patients with seasonal or perennial allergic rhinitis [12,15]. Desloratadine is the major biologically active metabolite of loratadine, with in vitro and in vivo anti-inflammatory effect [16].

In our study we evaluate the effect of H1 antihistamines on nasal congestion and on plasmatic levels of IL-6 and IL-8 in patients with persistent allergic rhinitis, after 4 weeks treatment, during continuous natural exposure to allergens.

Material and method

Patients

79 patients with persistent allergic rhinitis (PAR) were included. A detailed clinical examination was carried out for each patient. The diagnosis of PAR was done according to international guidelines, based on history and skin prick test (SPT). The patients signed an informed consent prior to study entry. Exclusion criteria were: acute upper respiratory infections within the previous 30 days, use of antibiotics, intranasal or oral corticosteroids and

H1 antihistamines within the previous 4 weeks, nasal polyps.

The patients were randomised in 2 groups, each one treated with Levocetirizine 5 mg/day and Desloratadine 5 mg/day for 4 weeks. This was the only allowed treatment during the study. The patients' evaluation was performed before and after 4 weeks of treatment.

Nasal symptoms

We followed the nasal symptoms: rhinorrhea, nasal congestion, sneezing, nasal and ocular itching before and after 4 weeks treatment. Each symptom was evaluated on a scale from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe) and after that we calculated the total symptoms score (TSS). A total score ≥ 6 means a moderate/ severe rhinitis, while a score <6 means a mild one.

Skin prick test (SPT)

Allergy was assessed by the presence of sensitisation to major classes of allergens, by performing the SPT. Allergens panel included: house dust mites, grasses mix, weeds mix, betulaceae, moulds mix, cat and dog dander. Allergens extracts (Stalergens, France) in concentration 100 IR/ml were used. SPT were performed on the volar surface of forearm, using as positive control standard histamine extract and as negative control standard saline solution. The results of SPT were evaluated after 15 minutes. A wheal diameter > 3 mm was considered a positive result.

Plasmatic cytokines level

Serum samples were obtained before and after 4 weeks treatment. The blood samples (5 ml) were spun in the first hour, followed by serum separation. The samples were stored at -80°C until the determination of the concentration. Determination of IL-6 and IL-8 was performed using ELISA technique (Quantikine R&D, USA kit). The samples and standard dilutions were assayed according to the manufacturer's instructions.

Statistical analysis.

The obtained data were analysed using SPSS 15 and GraphPad Prism 4 programs. The data are presented as means and SD. Differences on evaluated parameters were assessed within groups by Wilcoxon Signed Rank test and between groups by Mann Whitney test. The coefficients of correlation Pearson and Spearman were calculated to highlight different correlations between the studied parameters. P values <0.05 were considered statistically significant.

Results

Patients

The demographic data of the patients are presented in table no. 1.

Parameter		Total (n=79)	Desloratadine (n=39)	Levocetirizine (n=40)
Age		30.44±9.90	32.89±12.17	28.05±6.32
Sex	M	50.6% (40)	43.6% (17)	57.5% (23)
	F	49.4% (39)	56.4% (22)	42.5% (17)
Environment	Urban	83.5% (66)	82.1% (32)	85% (34)
	Rural	16.5% (13)	17.9% (7)	15% (6)
Severity	Mild	29.1% (23)	33.3% (13)	25% (10)
	Moderate/severe	70.9% (56)	66.7% (26)	75% (30)
Onset		3.39 years	3.72 years	3.07 years
Sensitisation	Indoor	81% (64)	94.9% (37)	67.5% (27)
	Outdoor	74.7% (59)	66.7% (26)	82.5% (33)

Table 1. Patients' demographic data

From the total of 79 patients, 40 patients received Levocetirizine 5 mg/day, while 39 patients were under treatment with desloratadine 5 mg/day. The average age was 30.44±9.90 years. 50.6% were male and 49.4% were female. Most of the patients (83.5%) were from urban environment, while only 16.5% were from rural areas. 56 of the patients (70.9%) presented a moderate/severe form of rhinitis, while 29.1% presented a mild disease.

64 (81%) were sensitized to indoor allergens, while 59 patients (74.7%) were sensitized to outdoor allergens (pollen). No statistically significant differences between the groups regarding sex ratio (p=0.21), environment (p=0.72) or the severity of rhinitis (p=0.41) were obtained.

Nasal symptoms

There is no statistical significant difference between Desloratadine and Levocetirizine groups regarding the baseline TSS (8.35 vs 8.67, p=0.79). After 4 weeks treatment the TSS significantly decreased in both Desloratadine (8.35 vs 1.97, p=0.0001) and Levocetirizine (8.67 vs 1.97, p=0.0001) groups. The intergroup analysis revealed no statistical difference between Levocetirizine and Desloratadine (p=0.85).

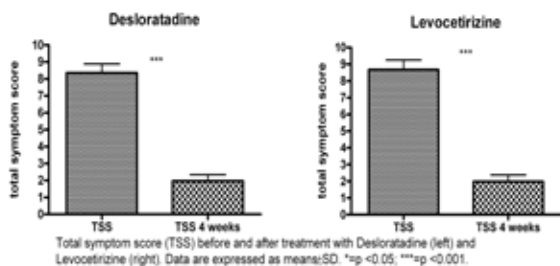


Figure 1. TSS in both groups before and after treatment

It is well known that H1 antihistamines influence especially rhinorrhea, sneezing and nasal itching. In this study both Desloratadine and Levocetirizine reduced these symptoms after 4 weeks treatment (see fig. no. 2). The comparison between the groups revealed no statistical significance for any men-

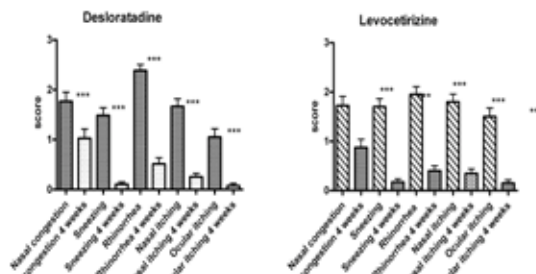


Figure 2. Symptoms score in both groups before and after treatment

Plasmatic level of cytokines

IL-6 was detected in all patients' serum, while IL-8 was present only in 96.2% of the patients, in 3 patients it was under the detectable value. IL-6 was decreased under minimal accepted value of this method (0.447-9.96 pg/ml) in 4 patients both before and after treatment. No patients had increased plasmatic levels compared with the maximal accepted values. Regarding IL-8 this was increased over 32.5 pg/ml (limits 0-32.5 pg/ml) in 3 patients before treatment. In 2 patients the undetectable values are also maintained after treatment.

IL-6 plasmatic level is negative correlated with pollen sensitisation (p=0.034), but it is not correlated with sensitisation to indoor allergens (p=0.65). Regarding IL-8 there is no correlation between its

plasmatic level and sensitisation to indoor or outdoor allergens ($p=0.71$, respectively $p=0.71$).

Both Desloratadine 5 mg/day and Levocetirizine 5 mg/day reduce the mean values of IL-6 after 4 weeks treatment. The decreasing is statistically significant both for Desloratadine (1.68 vs 1.36, $p=0.0038$) and Levocetirizine (1.19 vs 1.006, $p=0.0097$). The intergroup analysis revealed no significant difference between these two drugs ($p=0.36$).

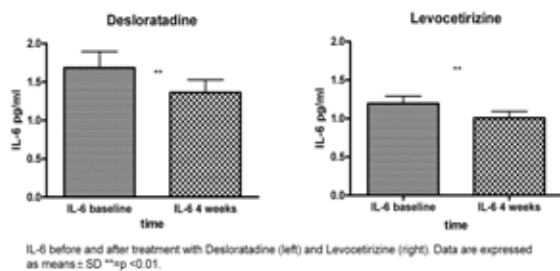


Figure 3. IL-6 level before and after treatment

IL-8 decreased under H₁ antihistamines treatment, but the reduction of the plasmatic level is significant only in Levocetirizine group (8.90 vs 6.90, $p=0.0003$). In Desloratadine group IL-8 the level also decreased but not in a significant manner (6.34 vs 5.79, $p=0.36$). The comparison between 2 groups revealed no significant difference between Levocetirizine and Desloratadine ($p=0.25$). The level of IL-6 and IL-8 is not correlated with the onset of the disease both in Levocetirizine ($p=0.39$, respectively $p=0.51$) and Desloratadine ($p=0.63$, respectively $p=0.77$) groups.

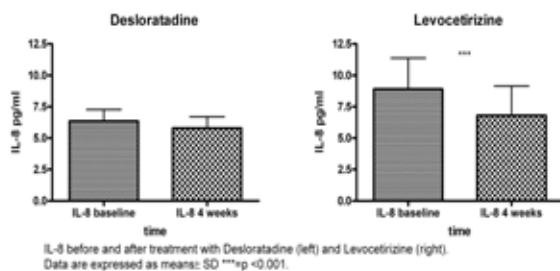


Figure 3. IL-8 level before and after treatment

Discussion

The effects of two H₁ antihistamines, Levocetirizine and Desloratadine on nasal symptoms, especially nasal congestion, and on plasmatic levels of pro-inflammatory cytokines, in patients with allergic rhinitis before and after treatment were evaluated in this study.

Allergic rhinitis is characterized by a Th₂ response, which finally induces the inflammation of nasal mucosa. The nasal congestion is due to different factors: mucosal inflammatory edema,

mucus hypersecretion and vascular congestion. In this response are involved mediators which belong both to the early and late phase of allergic inflammation [17]. Although the eosinophil is the major cell involved in late phase of allergic inflammation, there are several data which show the involvement of other inflammatory cells [4,17].

There are data regarding the increased level of pro-inflammatory cytokines (IL-1, IL-6, IL-8 and TNF- α) in patients with allergic rhinitis [17,18]. The cytokines activate the immune cells and associated with IgE production contribute to enhance the allergic inflammation [18]. Bachert in his studies [7,18] and also Ohkubo [9] showed high levels of IL-6 and IL-8 in nasal secretion after specific allergen challenge. In our study the levels of IL-6 and IL-8 are normal, but the determinations were performed using serum samples not nasal secretion in which the mediators appear for the first time.

On the other hand in this study the patients were under continuous exposure to allergens, not after a single challenge like in the abovementioned studies. The results from this study confirm Bachert's study [19], which revealed that IL-8 has no changed values in patients with allergic rhinitis to pollen under continuous exposure for 6 weeks compared with healthy volunteers. In this study a negative correlation was noticed between the IL-6 level and pollen sensitisation. Also this correlation was not present in case of indoor allergens sensitisation. This could have an explanation, because the patients sensitised to pollen, included in this study were evaluated during the pollen season, after the onset of allergic inflammation. So it could be said that IL-6 is a pro-inflammatory mediator involved in the early phase after allergen exposure, which helps in allergic inflammation onset. IL-8 is a chemoattractant factor for neutrophils, but it is involved later in allergic inflammation, compared with IL-6 [9,20].

Allergic inflammation decreasing can be clinically evaluated following the nasal congestion, a symptom that was observed in this study. There are several data regarding the 2nd generation H₁ antihistamines effect on nasal congestion [21,22,23]. In the present study both Levocetirizine and Desloratadine decrease all the allergic rhinitis symptoms, being effective also on nasal congestion. There is no difference between 2 drugs in this study, although previously it was showed that Levocetirizine improves the nasal congestion better than other antihistamines [12,15,24]. Moreover in this study the reduction of nasal congestion by Desloratadine was demonstrated like in Horak's study [25].

In vitro studies revealed an influence of H₁ antihistamines on pro-inflammatory cytokines. So in vitro studies showed that Cetirizine and Levo-

cetirizine inhibit neutrophil releasing of IL-8 and TNF- α [24]; it is well known that the neutrophil is involved in the early phase after allergen challenge and IL-8 is the main chemoattractant factor for it. In this study both Levocetirizine 5 mg/day and Desloratadine 5 mg/day decrease IL-6 plasmatic level after 4 weeks treatment. Regarding IL-8 only Levocetirizine decreases the level and Desloratadine has no influence on it. Our data confirm the observation of Ciprandi et al. [12] after 2 weeks treatment with H1 antihistamines. In our study we followed the plasmatic levels of IL-6 and IL-8 after 4 weeks treatment because some authors who revealed an anti-inflammatory effect of the drugs in vitro supposed that this effect could be sustained after a prolonged treatment.

Deruaz et al. assessed the comparative effect of Levocetirizine 5 mg and Desloratadine 5 mg, single doses, in patients with allergic rhinitis to grass pollen. They followed the symptoms and also the levels of IL-4, IL-5, IL-8, eotaxine and ECP in nasal lavage fluid. No mentioned antihistamines have any influence on cytokines level, but the authors cannot exclude their possible anti-inflammatory effect after a prolonged administration [24]. In this study a decrease of IL-6 and IL-8 was noticed after Levocetirizine 4 weeks treatment and a decrease of IL-6 after Desloratadine, which confirm the assumption of the above mentioned study.

In conclusion we can say that Levocetirizine and Desloratadine decrease all the symptoms of allergic rhinitis, including nasal congestion after 4 weeks treatment. Levocetirizine has an anti-inflammatory effect in vivo, demonstrated by decreasing of IL-6 and IL-8 levels. Desloratadine presents an anti-inflammatory effect in early phase because it decreases only the IL-6 level.

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