

Cetirizine treatment of rhinitis in children with pollen allergy: evidence of its antiallergic activity

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Summary

Background Cetirizine is an antihistamine, largely used in the treatment of allergic rhinoconjunctivitis, which also exerts anti-allergic activity.

Objective To evaluate cetirizine as treatment for children with rhinitis due to pollen allergy, and to evaluate its anti-allergic activity in such a clinical condition.

Methods The study was designed as parallel groups, double-blind, placebo-controlled, randomized. Twenty allergic children were enrolled and subdivided in two groups, receiving a 4 week treatment during the pollen season. The following parameters were monitored: clinical symptoms evaluated by the allergist before and after treatment and by the patients through a daily diary card, inflammatory cells count, expression of ICAM-1 on nasal epithelial cells, inflammatory mediator levels in nasal lavage and peripheral blood before and after treatment, and pollen counts.

Results This study shows that cetirizine treatment is able to reduce: clinical symptoms ($P < 0.01$), inflammatory cell infiltrate ($P < 0.03$), ICAM-1 expression on epithelial cells ($P < 0.05$), and soluble ICAM-1 ($P < 0.05$) and ECP ($P < 0.05$) in nasal lavage.

Conclusion Cetirizine is able to clinically improve nasal symptoms due to pollen allergy and to reduce allergic inflammation, which is related to allergen exposure.

Keywords: allergic rhinitis, children, cetirizine, antiallergic activity, symptoms, inflammation, adhesion molecules, mediators

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Introduction

Allergic rhinitis is the most common immune-mediated disease and its prevalence is progressively increasing. The allergic reaction is actually considered not only as an immediate short-lived phenomenon, but rather as a dynamic process, characterized basically by an inflammatory response. Both clinical and experimental evidence supports a strict relationship between IgE-mediated reactions and the resulting immune-mediated inflammatory process [1]. In particular, one of the hallmarks of allergic reaction is the eosinophil infiltrate: in fact, eosinophil presence in the nasal smear is particularly suggestive of an allergic reaction.

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Allergen exposure induces mast cells activation and release of mediators and cytokines able to induce inflammatory cell recruitment and activation at the target organ level [2]. In this context, the adhesion molecule system is largely involved in cell–cell and cell–matrix interaction, allowing inflammatory cell recruitment and selective migration throughout endothelium across the matrix to the epithelium [2]. Activated mast cells release cytokines (such as IL-4, IL-5, IL-8, $\text{TNF}\alpha$) able to upregulate expression of adhesion molecules [2]. As recently demonstrated, epithelial cells express ICAM-1 (intercellular adhesion molecule-1) upon allergen exposure [3,4]. ICAM-1 is the natural ligand of LFA-1 and Mac 1, the β_2 integrins expressed on leucocytes, including eosinophils, the hallmark cells of allergic inflammation [5]. Thus, eosinophil infiltration of epithelium and the consequent epithelial damage can be partly explained.

Table 1. Spearman's correlation (*P*-value) between parameters

	EOS	NEU	ICAM-1	Serum ICAM-1	Serum ECP	Nasal ICAM-1	Nasal ECP
Clinical score	0.02	0.01	0.04	NS	NS	NS	NS
	EOS	0.03	0.001	NS	NS	0.02	NS
		NEU	0.05	NS	NS	NS	NS
			ICAM-1	NS	0.01	0.03	NS
				Serum ICAM-1	NS	NS	NS
					Serum ECP	NS	NS
						Nasal ICAM-1	0.001

In fact, it has been demonstrated that histamine stimulus is not able to induce eosinophil infiltration and ICAM-1 expression on epithelial cells at conjunctival level [7].

Cetirizine exerts different activities on eosinophil functions, both concerning activation (i.e. metabolic activities and release of mediators) and migration from the blood stream into the mucosa. Cetirizine inhibited the generation of superoxide anion PAF-induced, vacuolization after allergen challenge and cytotoxicity to complement coated *Schistosomula* of *Schistosoma mansoni* [13].

As far as migration process is concerned, it has been demonstrated that cetirizine inhibited *in vitro* eosinophil PAF-induced hyperadherence to human umbilical vein endothelial cells (HUVEC) [14] and also *in vivo* eosinophil accumulation after allergen exposure at cutaneous [15], nasal [8], conjunctival [7] and bronchial [16] level. This inhibitory effect on eosinophil migration and accumulation at allergic sites is, at least partially, due to its modulation of adhesion molecules' expression and/or function at mucosal barrier level.

The present study further indicates that cetirizine reduces eosinophil migration and activation at the site of allergic reaction. In fact a less abundant eosinophil infiltrate and lower ECP levels recovered by nasal lavage occurred after cetirizine treatment. That cetirizine effect on eosinophil is likely, on the basis of the literature [13,16] evidences, thus a possible direct effect on eosinophil can be suggested.

In addition, it has been demonstrated that cetirizine reduced *in vivo* ICAM-1 expression at epithelial (nasal and conjunctival) level [7,8]. On the basis of such evidence, a new different cetirizine mechanism of action may be perspected: reduced ICAM-1 expression induces a minor possibility of eosinophil to adhere to epithelium [7,8,17,18].

The reduced epithelial ICAM-1 expression may be due to a possible cetirizine effect on epithelial cells, and to an indirect cetirizine effect on eosinophil, since eosinophil are

both less abundant at mucosal level and less activated (i.e. reduced ECP release). In fact, it was demonstrated that ECP *per se* upregulates ICAM-1 expression [19]. A substantiated confirm of this hypothesis derives from reduced values of soluble ICAM-1 recovered by nasal lavage. ICAM-1 may be shed both by epithelial cells and leucocytes [20]; so this evidence may reflect both a reduced epithelial ICAM-1 synthesis and/or a diminished shedding by eosinophils, which are less abundant at mucosal level and at the same time less activated. A clear relationship between ICAM-1 expression on epithelial cells and number of eosinophils is in fact demonstrable. On the other hand, the unmodified value of seric soluble ICAM-1 and ECP confirms the fact that inflammation during rhinitis is mainly restricted to the site of allergic reaction. These combined actions on ICAM-1 expression on epithelial cells and eosinophils, in terms of locomotion and activation, suggest cetirizine as a compound able to protect the epithelium during allergic inflammation.

The results of the study suggest that, in addition to its effectiveness on conjunctival and nasal symptoms, cetirizine reduces allergic inflammation.

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