

Effects of Fexofenadine on Inflammatory Mediators in Nasal Lavage Fluid in Intermittent Allergic Rhinitis

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■ Abstract

Objective: Allergic rhinitis, a disease that impairs quality of life, is characterized by inflammation due to an allergic reaction. Fexofenadine is a second-generation histamine receptor blocker well known for its potent interaction with this inflammatory process. The main aim of this study was to further clarify the anti-inflammatory effects exerted by fexofenadine in patients with intermittent allergic rhinitis.

Methods: Twenty patients with intermittent allergic rhinitis due to birch and mugwort pollen were enrolled. Fexofenadine was administered once a day at a dose of 120 mg. Clinical improvement was assessed by a symptom score, and nasal airway flows were measured by anterior rhinomanometry at baseline and after 2 weeks of treatment with fexofenadine. Nasal smears were tested for eosinophils and nasal lavage fluid were examined for histamine, cysteinyl leukotrienes, soluble intercellular adhesion molecule-1, eosinophil cationic protein, and albumin by enzyme-linked immunosorbent assay. All the tests were performed during the pollen season.

Results: Fexofenadine induced a significant improvement in nasal and ocular symptoms ($P < .001$), nasal edema and secretion ($P < .001$), and nasal airway flow ($P < .001$). The clinical improvement was related to a significant reduction in all inflammatory mediators ($P < .01$ in all cases).

Conclusion: This study demonstrates that fexofenadine is able to mediate significant changes in different nasal lavage markers from patients with intermittent allergic rhinitis. The changes observed in the markers analyzed in both nasal secretions and serum are attributable to the anti-inflammatory effects of fexofenadine in vivo.

Key words: Fexofenadine. Intermittent allergic rhinitis. Inflammation.

■ Resumen

Objetivo: La rinitis alérgica, una enfermedad que afecta a la calidad de vida, se caracteriza por la inflamación causada por una reacción alérgica. La fexofenadina es un bloqueante del receptor de histamina de segunda generación bien conocido por su potente interacción con el proceso inflamatorio. El principal objetivo de este estudio fue clarificar los efectos antiinflamatorios ejercidos por la fexofenadina en pacientes con rinitis alérgica intermitente.

Métodos: Se reclutaron veinte pacientes con rinitis alérgica intermitente debido a polen de abedul y artemisia. Se administró fexofenadina una vez al día a una dosis de 120mg. La mejoría clínica fue evaluada por puntuación de síntomas, y el flujo de la vía aérea nasal se evaluó por rinomanometría anterior basalmente y después de 2 semanas de tratamiento con fexofenadina. Los frotis nasales se analizaron para eosinófilos y el fluido del lavado nasal evaluado para histamina, cisteinil leucotrienos, molécula de adhesión intracelular soluble-1, proteína catiónica del eosinófilo, y albúmina por enzimoimmunoanálisis. Todas las pruebas se realizaron durante la época polínica.

Resultados: La fexofenadina indujo una mejoría significativa en los síntomas nasales y oculares ($P < .001$), edema y secreción nasal ($P < .001$), y el flujo de la vía aérea nasal ($P < .001$). La mejoría clínica se relacionó con una reducción significativa en los mediadores inflamatorios ($P < .01$ en todos los casos).

Conclusión: Este estudio demuestra que la fexofenadina es capaz de mediar cambios significativos en diferentes marcadores en el lavado nasal de pacientes con rinitis alérgica intermitente. Los cambios observados en los marcadores analizados tanto en las secreciones nasales como en el suero son atribuibles a los efectos anti-inflamatorios de fexofenadina in vivo.

Palabras clave: fexofenadina, rinitis alérgica intermitente, inflamación

Introduction

In recent years, allergic rhinitis has attracted increasing attention due to its impact on quality of life and diseases such as asthma, as documented in the Allergic Rhinitis and its Impact on Asthma (ARIA) document [1]. The pathophysiology of allergic rhinitis symptoms is complex and characterized by mucosal infiltration with inflammatory cells and a type 2 helper (T_H2) cell-derived cytokine pattern [2]. The disease is also characterized by sustained tissue inflammation as a result of an immunoglobulin (Ig) E-mediated hypersensitivity reaction [3-5]. At the cellular level, histamine also acts on inflammatory cells, leading to the release of mediators such as leukotrienes and cytokines and increasing the expression of intercellular adhesion molecule (ICAM)-1 on epithelial cells [6,7]. Since mediator release into the airway lumen is an important factor in the pathogenesis of airway disease, lavage techniques have been used to study the underlying mechanisms of allergic rhinitis [4,5,8].

Although antihistamines are widely used in symptomatic treatment [9-12], their interactions have not been completely understood. Recent studies have shown that several antihistamines possess nonreceptor-mediated anti-inflammatory properties, suggesting additional effects in the management of allergen-induced inflammation [13]. Examples of histamine 1 (H_1) receptor antagonist effects that are unrelated to receptor antagonism are the degranulation of mast cells [14], the release of oxygen radicals from eosinophils and neutrophils [15], the generation of lipid mediators, eosinophil migration [16], the stimulation of ciliary motility, cytokine synthesis, and the inhibition of calcium influx. It is now evident that cysteinyl leukotrienes (CysLTs) such as LTC₄, D₄, and E₄, together with adhesion molecules such as soluble ICAM (sICAM), and eosinophil cationic protein (ECP) are proinflammatory mediators for airway diseases such as bronchial asthma and allergic rhinitis [17].

Fexofenadine is a carboxylic acid metabolite of terfenadine and a highly specific H_1 receptor antagonist. Its efficacy has been demonstrated in double-blind, placebo-controlled trials in patients with seasonal allergic rhinitis [12], with a rapid onset of action and a significant improvement in symptoms [18]. The aim of the current study was to investigate the clinical improvement in nasal symptoms and changes in concentrations of sICAM-1, CysLTs, histamine, albumin, eosinophils, and ECP in nasal secretions from symptomatic patients before and after 2 weeks of treatment with fexofenadine in vivo during the pollen season.

Materials and Methods

Participants

Twenty adults (11 women) with allergic rhinitis due to birch (n=8) and mugwort pollen (n=12), aged between 19 and 65 years (mean \pm SEM age, 32.2 \pm 12 years), were included in the study. Antiallergic drugs were stopped 6 weeks prior to enrollment. Exclusion criteria were the presence of systemic disease or conditions other than nasal allergic inflammation, use of immunotherapy, and pregnancy. Allergic rhinitis due to pollen was defined as the presence of typical clinical symptoms (airway obstruction, sneezing, itching, and rhinorrhea) for more

than 2 years. Sensitivity was confirmed by positive skin prick tests, specific serum IgE (CAP allergy class, >2; Pharmacia CAP System; Pharmacia AB, Uppsala, Sweden), and total IgE. Two patients had mild seasonal asthma and were maintained on low-dose inhaled steroids and bronchodilators as needed.

Study Design

After the baseline visit, patients were treated with fexofenadine (120 mg once daily) for 14 days. The treatment began 1 week after the start of the pollen season. Pollen count was registered over the whole study period. The study was approved by the local ethics committee at the Humboldt University of Berlin and all the participants gave their written informed consent. An open trial design was chosen since a placebo group could not be used for ethical reasons.

Symptom Assessment and Rhinomanometry

Nasal symptom scores and nasal airway function were assessed at baseline and 14 days after treatment. The degree of nasal airway obstruction was assessed by nasal peak inspiratory flow, expressed in cm³/s, and nasal airway resistance, expressed in Pa/cm³/s, measured for each nostril by active anterior rhinomanometry (Rhinotest MP 500; Allergopharma Joachim Ganzer KG, Reinbeck, Germany) at a pressure of 150 Pa.

Patients were instructed to record their daily symptoms on diary cards. The clinical scores for the 4 major nasal symptoms (airway obstruction, sneezing, itching, and rhinorrhea) and ocular symptoms were graded according to a 4-point symptom severity scale (0, no symptoms; 1, mild symptoms with minimal awareness; 2, moderate or tolerable symptoms; and 3, severe symptoms that are difficult to tolerate and interfere with daily activities and sleeping). The number of sneezes per day was counted and converted into a score according to the following scale: 0, 0 sneezes; 1, 1-4 sneezes; 2, 5-9 sneezes; and 3, \geq 10 sneezes. The total nasal symptom score (range, 0-12) was calculated by adding up these scores for each patient at baseline and after treatment. Rhinoscopic examinations were performed by the same physician at baseline and 14 days posttreatment to confirm nasal blockage/edema, rhinorrhea/secretion, and irritation using a 4-point rating scale (0, absent; 1, mild; 2, moderate; and 3, severe).

Laboratory Tests

Nasal Lavage

Nasal lavage was performed by instilling 5 mL of sterile saline solution (preheated to 37°C) into each nasal cavity (sealed with foam rubber) using a tube connected to a syringe. After 10 seconds, fluid samples were collected in a polypropylene tube by repeated aspiration from both nasal cavities and immediately put on ice. After centrifugation at 1000 g for 10 minutes at 4°C and removal of cellular elements, the supernatants were divided into aliquots for the various assays and stored at -80°C until analysis.

Assessment of Mediators

The following tests were performed according to the manufacturer's instructions. All peptides were measured in

duplicate in 50 μL lavage fluid using highly specific, competitive commercial enzyme-linked immunoabsorbent assay (ELISA) kits. sICAM-1 was calculated to ng/mL (minimum detectable concentration, 0.25 ng/mL) (Immunotech; Beckman Coulter Company, Florida, USA) and CysLTs (LTC₄, LTD₄, LTE₄) to pg/mL of lavage fluid (minimum detectable concentration, 3.24 pg/mL) (Enzyme Immunoassay; Cayman Chemical Company, Ann Arbor, Michigan, USA).

ECP in nasal fluid and serum was determined by fluorescent enzyme immunoassay using the CAP system (Pharmacia AB). The detection limit was 0.5 ng/mL and interassay variation was less than 5.9% (UniCAP; Pharmacia AB).

Human serum albumin (HSA) in the lavage samples was determined by ELISA. Immunosorbent microtiter plates (NUNC GmbH, Langensfeld, Germany) were coated with HSA (5 $\mu\text{g}/\text{mL}$) and incubated overnight at 4°C. Nonspecific binding sites were blocked with 1% bovine serum albumin incubated for 1 hour at room temperature and washed with Tris(hydroxymethyl)-aminomethane (TRIS) buffer. Appropriate dilutions of the samples and HSA standard (Sigma Chemicals, Deisenhofen, Germany) were placed on a Greiner microtiter plate. Purified mouse anti-HSA (ImmunoPure Mouse Monoclonal Anti-human Serum Albumin Assay Reagent, Pierce Protein Research Products, Rockford, Illinois, USA) at a dilution of 1:100 000 were added and incubated for another hour at 37°C (detection limit, 10 $\mu\text{g}/\text{mL}$). Next, 150 μL were transferred to the coated NUNC plate and incubated for 1 hour and then washed 3 times with TRIS buffer and incubated with alkaline phosphatase-conjugated Affinipure goat anti-mouse IgG (Dianova, Hamburg, Germany) (dilution, 1:1000) for 1 hour. The wells were then washed 4 times and the reaction was developed with p-nitrophenyl phosphate (Sigma Chemicals); absorbance readings were taken at 405 nm. The assay standard curve for HSA ranged from 9.75 (minimum detectable concentration) to 10.000 ng/mL. For histamine analysis, the supernatants were assayed after protein precipitation with a volume of 2% perchloric acid by means of an automated fluorometric technique capable of detecting 0.5 ng/mL of histamine [19]. All biochemical measurements were done in a blinded fashion.

Nasal Cytology

Nasal smears were taken from the inferior turbinate at the baseline visit and after treatment using a cotton-wool swab dampened with physiological saline. The sampled cells were transferred to microscope slides by gentle rolling. After air drying, the samples were stained using the May-Grünwald-Giemsa technique. Eosinophils were counted per 100 cells and expressed as a percentage of total cell counts. All specimens were examined by the same microscopist in a blinded fashion.

Statistical Analysis

Two-way analysis of variance and the *t* test for paired data were used to compare mean changes in patients before and after treatment. The *t* test was also used to analyze differences for paired and unpaired data. Data were expressed as mean \pm SEM values. Clinical scores, concentrations of sICAM-1, CysLTs, ECP, histamine, and albumin in nasal lavage fluid, and

eosinophil counts were compared using the Wilcoxon signed rank test (pre/post treatment).

The Spearman correlation coefficient (*r*) was calculated to analyze possible correlations between sets of 2 parameters. Statistical tests were performed using a standard computer package program (SPSS/PC, version 16.0; SPSS Inc., Chicago, Illinois, USA) and a *P* value of .05 was considered significant in all cases.

Results

Clinical Data and Rhinomanometry

All patients completed the study and no adverse effects were reported. The mean daily pollen counts — 325/ m^3 of air (range, 22–2420/ m^3) during the birch period and 35/ m^3 of air (range, 10–85/ m^3) during the mugwort pollen period — were high enough throughout the study period to induce clinical symptoms. Treatment with fexofenadine for 2 weeks resulted in a significant improvement of symptoms (as rated by patients on dairy cards) ($P < .001$) and clinical signs (edema and hypersecretion) as assessed by the physician ($P < .001$) (Table). The mean total nasal symptom score decreased from 10.8 at baseline to 1.8 posttreatment ($P < .001$). The mean eye symptom score also decreased (from 2.5 to 0.25). The treatment also led to a significant decrease in nasal airway flow ($P < .001$) and resistance ($P < .001$) (Table).

Table. Changes in Clinical Parameters and Nasal Lavage Markers Following 2 Weeks of Treatment With Fexofenadine in Patients With Allergic Rhinitis During the Pollen Season^a

	Fexofenadine Treatment (120 mg Once Daily)	
	Before	After
Nasal symptom score ^b		
Obstruction	2.7 \pm 0.12	0.85 \pm 0.16 ^c
Rhinorrhea	2.75 \pm 0.12	0.75 \pm 0.14 ^c
Sneezing	2.65 \pm 0.13	0.45 \pm 0.11 ^c
Itching	2.7 \pm 0.12	0.5 \pm 0.11 ^c
Anterior rhinomanometry score		
Edema	2.75 \pm 0.09	0.95 \pm 0.13 ^c
Secretion	2.6 \pm 0.11	0.35 \pm 0.15 ^c
Nasal air flow, ccm/s	227.8 \pm 27.5	542.25 \pm 40.8 ^c
Nasal lavage mediators		
CysLT, pg/mL	279.75 \pm 77.9	122.1 \pm 40.8 ^d
sICAM, ng/mL	0.89 \pm 0.3	0.29 \pm 0.08 ^e
Histamine, ng/mL	5.27 \pm 1.01	2.39 \pm 0.3 ^e
HAS, $\mu\text{g}/\text{mL}$	702.3 \pm 136.8	323 \pm 64.7 ^e

Abbreviations: CysLT, cysteinyl leukotrienes; HAS, human serum albumin; sICAM, soluble intercellular adhesion molecule-1.

^aValues are given as mean \pm SEM.

^bGraded according to a 4-point symptom severity scale (0, no symptoms, 1, mild symptoms with minimal awareness, 2, moderate or tolerable symptoms, and 3, severe symptoms that are difficult to tolerate and interfere with daily activities and sleeping).

^c $P < .001$, calculated using the *t* test.

Mediator Levels in Nasal Lavage Fluid

There was a significant decrease in all mediator levels in nasal lavage fluid (Table) and also in the percentage of eosinophils (Figure 1) in nasal smears after 2 weeks of treatment with fexofenadine. There was also a trend, albeit without statistical significance, toward a decrease in serum ECP levels after treatment (Figure 2B). The decrease for ECP in nasal lavage fluid, in contrast, was significant (Figure 2A). Prior to treatment, the percentage of eosinophils in nasal smears was low (0%-15%) in 5 patients and high (17%-88%) in 15 patients. No differences were found between the birch pollen and the mugwort pollen groups in terms of clinical results or nasal lavage mediator concentrations and changes.

Correlations

We found a significant correlation between the total symptom score and a reduction in the release of mediators (except CysLTs) and eosinophil cell count in nasal lavage fluid after treatment with fexofenadine. ECP concentrations in nasal lavage fluid and serum also showed a significant correlation ($r=0.48$, $P<.01$).

Discussion

Our data describe the *in vivo* effects of fexofenadine on clinical symptoms and nasal lavage levels of surrogate parameters of inflammatory and immune response in a population of adult patients with intermittent allergic rhinitis.

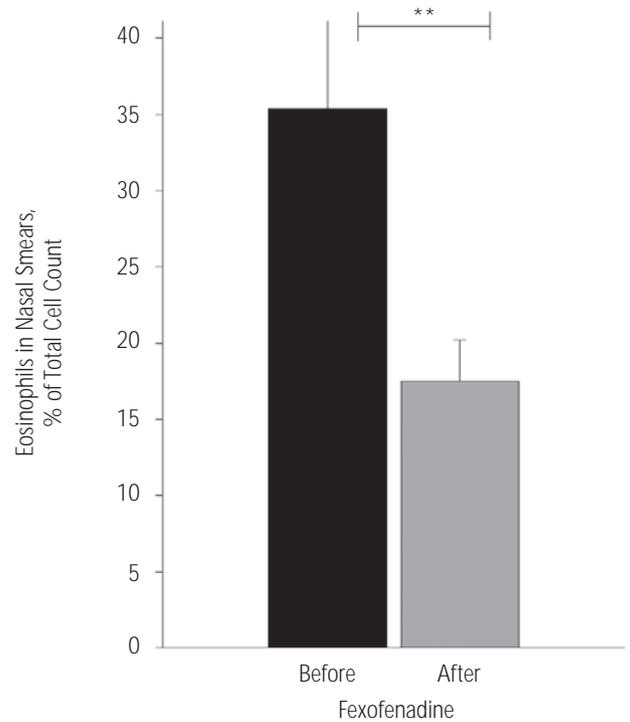


Figure 1. Effect of 2 weeks of treatment with fexofenadine (120 mg once daily) on eosinophil counts in nasal smears in 20 patients with seasonal allergic rhinitis during the pollen season. A significant decrease was found for the 20 patients. The results (mean score \pm SEM) were obtained before and after treatment and compared using the Wilcoxon test (** $P<.01$).

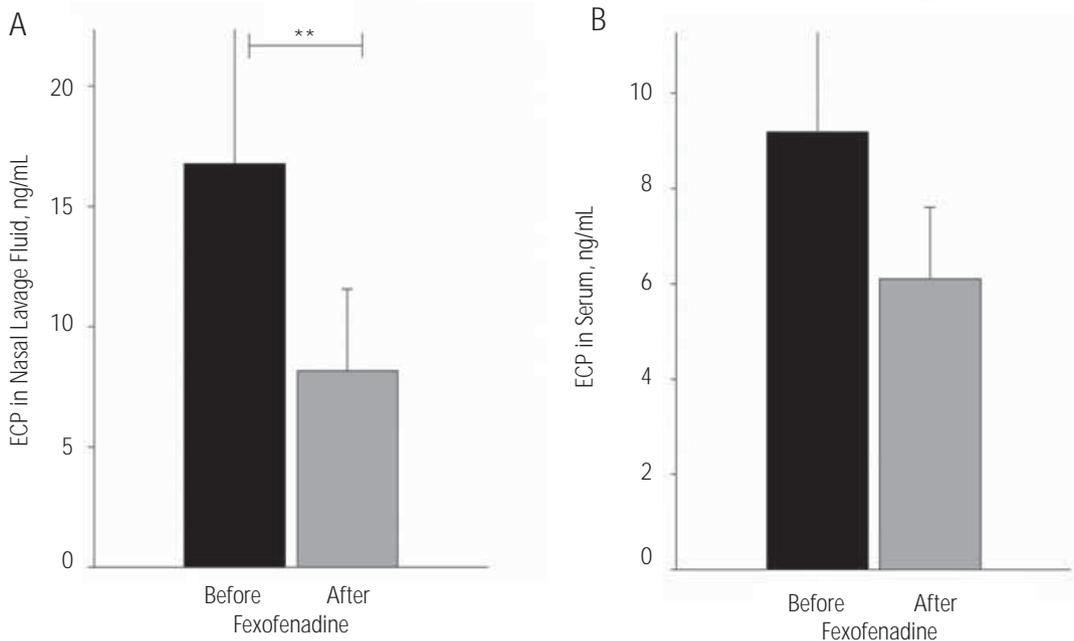


Figure 2. Effect of 2 weeks of treatment with fexofenadine (120 mg once daily) on eosinophil cationic protein (ECP) concentrations in nasal lavage fluid (A) and serum (B) from patients with seasonal allergic rhinitis during the pollen season. A significant decrease in ECP concentrations was found in nasal lavage fluids only during the pollen season for the 20 patients. The results are expressed as mean values \pm SEM (** $P<.01$).

The administration of fexofenadine over 14 days resulted in a significant decrease in both nasal and conjunctival symptoms. These clinical effects are at least partly attributable to a significant decrease in sICAM-1, CysLTs, eosinophil numbers, and ECP in nasal lavage fluids. The trend toward a decrease in serum ECP levels might suggest accompanying systemic effects.

Allergic inflammation is associated with the release of several mediators, inflammatory cells, and the stimulation of C-afferent fibers [5,20,21]. The inflammatory response to allergens such as pollen, either by challenge in the laboratory or by natural exposure, is accompanied by the recruitment of inflammatory cells and the stimulation of nerves, followed by the release of mediators, cytokines, and neuropeptides [20,21], leading to the various symptoms of allergic rhinitis such as hypersecretion, nasal blockage, and sneezing.

In line with previous findings [22], fexofenadine was also well tolerated in our study, with no adverse effects being reported by patients. Furthermore, it was demonstrated that the baseline levels of CysLTs, s-ICAM, histamine, albumin, and ECP in nasal lavage fluid, and eosinophils in nasal smears were considerable in untreated atopic patients, correlating with an increased symptom score.

After treatment with fexofenadine, there was a significant reduction in the symptom score, in parallel with a decrease in nasal lavage mediator levels. A prominent finding was the fact that the increase in nasal flow and decrease in nasal resistance observed was correlated with a significant improvement in nasal leakage. Several *in vivo* and *in vitro* studies have demonstrated that fexofenadine inhibits allergen-induced inflammatory changes in allergic rhinitis by decreasing cellular infiltration and the activation of eosinophils, T cells, and mast cells in the nasal mucosa [23,24]. Ciprandi et al [25] studied various aspects of the antiallergic activity of desloratadine and levocetirizine over a 4-week period during the allergy season. After treatment with both antihistamines, there was a significant reduction in symptoms and nasal eosinophil counts. These findings are in line with those of the present study and suggest that antihistamines have anti-inflammatory properties in allergic rhinitis *in vivo*. It has been suggested that the reduction of mediator concentrations observed in these studies may be due to a reversal in increased vasopermeability induced by histamine rather than to a direct pharmacological effect on mast cells.

In this context, the findings of Marone et al [26] are of great interest in that they showed that fexofenadine inhibited the histamine-induced release of β -glucuronidase and interleukin 6. This effect, proven with alveolar macrophages, is probably H-receptor mediated. A similar effect might exist in the case of eosinophils and epithelial cells [27,28]. Since mediators such as prostaglandin D2, kinins, and leukotrienes are responsible for nasal obstruction, mainly by engorgement of the venous sinusoids, it can be assumed that modern antihistamines, including fexofenadine, are effective by reducing epithelial cell activation and thus causing a decreased accumulation of cells, particularly mast cells, eosinophils, and basophils. This mechanism would explain the reduction in CysLT, histamine, ECP, and sICAM-1 levels observed in our study as well as the significant reduction in nasal blockage. The trend toward a

decrease in serum ECP might be an additional hint that allergic rhinitis causes systemic effects.

Ciprandi et al [29] showed the capability of antihistaminic treatment of improving nasal airflow and inflammation in patients with perineal allergic rhinitis. In the present study, we have demonstrated comparable effects for adult patients with intermittent allergic rhinitis mediated by the well-described antihistamine fexofenadine.

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