The comparison of the efficacy of fluticasone propionate with cetirizine in perennial allergic rhinitis

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SUMMARY

Background: allergic rhinitis is an IgE mediated hypersensitivity reaction of the nasal mucosa characterized by nasal discharge, obstruction, and pruritus.

Patients and methods: in this study, 43 patients with perennial allergic rhinitis were enrolled in order to compare the efficacy of Fluticasone Propionate (FP), a corticosteroid nasal spray, with Cetirizine, a systemic oral antihistaminic preparation, which is supposed to have nonsteroidal anti-inflammatory activity. Cetirizine (10 mg daily as a single dose) was administered to 22 patient for 45 days. On the other hand, FP (400 μg/day) was administered into each nostril twice a day in the remaining 21 patients for 45 days.

Skin test was obtained from each patient before therapy. Total eosinophil count, eosinophil count in nasal smear, electrorhinomanometric investigation, PGE2 and ratio of LTC4 to LTD4 both in the serum and in the nasal secretions were determined before and after therapy.

In addition, percentage of eosinophils, and mast cells count in the biopsy specimens taken from anterior edge of middle concha were evaluated before and after therapy, and than the results were graded for each patients.

Results: when we compared the eosinophil count in nasal smear, eosinophil percentage and total eosinophil parameters between two groups, it was shown that FP was more effective than Cetirizine. On the other hand, when we compared the ratio of LTC4 to LTD4 in serum and nasal smear, level of PGE2 and mast cell and nasal airway resistance measured by ERM, there were non statistical difference between two groups.

Conclusion: these results suggest that FP and Cetirizine may be used alternatively in case of an adverse reaction to any of them.

Key words: Cetirizine. Fluticasone Propionate. Perennial allergic rhinitis.


INTRODUCTION

Allergic rhinitis is an IgE mediated hypersensitivity disease of nasal mucosa characterized by sneezing, nasal itching, rhinorrhea and nasal obstruction. For the last ten years, there has been an increase in the incidence of this health problem which is benign, but has a progressive disease. Although the cause of this increase is not known, it is presumed to be due to air pollution, increase of SO2, NO2 ratios and lost of ozone layer (1).

At present, antihistamines are among the most widely used pharmacological agents in the treatment of allergic rhinitis (2).

Cetirizine that is the main metabolite of hydroxyzine is a newly developed second-generation H1 receptor blocking agent. It is more selective than the others to the H1 receptors. At the same time, antiinflammatory effect of cetirizine has been suggested (3, 4).

In recent years, considerable attention has been paid to the treatment of the underlying inflammation of the nasal mucosa. Antiinflammatory agents such
as topical corticosteroids with high topical effects and minimal side effects, has proven to be very effective in the treatment of nasal allergy and hyperreactivity, especially in eosinophil dominated nasal inflammation (5).

In this study, the topical intranasal corticosteroid (Fluticasone Propionate) was compared with Cetirizine which is thought to have antiinflammatory effects. The effects on the histopathology of the nasal mucosa before and after treatment with these two different agents were evaluated. Eosinophil counting in nasal secretion, nasal and serum \( \text{PGE}_2 \) and \( \text{LTC}_4/\text{LTD}_4 \) levels, nasal airway resistance and total eosinophil counting were also determined.

**PATIENTS AND METHODS**

Fifty one patients (M/F = 21/30) referred to Departments of Otorhinolaryngology and Pediatric Allergy of Dokuz Eylül University Medical Faculty due to allergic rhinitis were included in this study that was conducted in between March 1996 and December 1997.

The inclusion criteria for the patients were:

1. No pathology except perennial allergic rhinitis on the routine otorhinolaryngologic examination.
2. History, compatible with perennial allergic rhinitis.
3. Physical examination, compatible with allergic rhinitis.
4. Patients with positive skin test at least to one allergen.
5. No treatment given for allergic rhinitis at least for the last two months.
6. Additionally, no other allergic disease like bronchial asthma which needed treatment before.
7. No additional sinonasal pathology found on paranasal sinus CT.

Eight patients (3 female and 5 male) were excluded, for not fitting all parameters and for not coming to follow up.

Thus, the study was completed with 43 patients (M/F = 16/17) with a mean age of 31.91 ± 41.55 years (range between 11 and 73). Before treatment and at the 45th day of treatment, total eosinophil and PNL count, eosinophil count in nasal smear, electrorhinomonometric (ERM) examination, \( \text{PGE}_2 \) and \( \text{LTC}_4/\text{LTD}_4 \) levels on nasal secretion and serum were determined in all patients. Similar before and after treatment, biopsy from front part of middle choncha was made and evaluated for percentage of eosinophils and mast cell count. Twenty two patients (M/F = 2/20) were given 10 mg of Cetirizine as a single daily dose for 45 days. Twenty one patients (M/F = 14/7) were given 400 µg intranasal Fluticasone Propionate (FP) daily, in two divided doses for 45 days. The type of treatment given to the patients was chosen randomly.

After the physical examination of skin test positive patients and evaluation of the nasal resistance by ERM, firstly nasal secretions were aspirated without any provocation for determining nasal mediators and nasal eosinophils. After that, biopsy specimens obtained were from the front parts of middle chonchae following topical anesthesia, and the samples were sent to Pathology department inside the formaline for evaluating of mediators. For the evaluation of total eosinophil count in the serum and in nasal secretions, 5 ml of venous blood and nasal secretion samples were sent to the Microbiology and Pediatric Allergy Laboratories, respectively.

Before and after treatment, nasal airway resistance was measured by using mercury NR6 Rhinomanometre with active anterior rhinomanometre. For the skin test, noninvasive, easily used epidermal prick test was used.

**Statistical Analysis**

In this study, T test for paired samples and Wilcoxon Matched Pairs Signed Ranks Test were used for effects of these two treatment on the evaluated parameters. For comparison of the effects of two treatment models, Mann-Whitney U and Wilcoxon Rank Sum W Tests were used.

**RESULTS**

When the pre and post treatment values of patients in Cetirizine group were compared, the percentage of eosinophils and mast cell count in the biopsy specimens were determined to decrease significantly (\( p < 0.05 \)).

Nasal eosinophil count, \( \text{LTC}_4/\text{LTD}_4 \) and \( \text{PGE}_2 \) levels decreased significantly (\( p < 0.05 \)), while PNL levels did not differ after treatment (\( p > 0.05 \)).

Total eosinophil count, \( \text{PGE}_2 \) and \( \text{LTC}_4/\text{LTD}_4 \) levels decreased significantly after treatment (\( p < 0.05 \)). In addition, both inspiratory and expiratory ERM values decreased significantly after treatment (table I).

When the pre and the post treatment values of the patients in the FP group were compared, post treatment changes in the parameters were just like those in the Cetirizine group, except nasal \( \text{LTC}_4/\text{LTD}_4 \) level which didn’t decrease significantly after treatment (\( p > 0.05 \)) (table II).
Table I

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After cetirizine treatment</th>
<th>p</th>
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<tbody>
<tr>
<td>Percent of eosinophil in biopsy</td>
<td>24.3%</td>
<td>79%</td>
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</tr>
<tr>
<td>Total eosinophil</td>
<td>468.2</td>
<td>352.3</td>
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<td>Nasal eosinophil</td>
<td>1.9</td>
<td>0.6</td>
<td>&lt; 0.05</td>
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<tr>
<td>Nasal PNL</td>
<td>7.6</td>
<td>6.7</td>
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</tr>
<tr>
<td>Mast cell count in biopsy</td>
<td>6.3</td>
<td>1.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Nasal LTC/D₄</td>
<td>45.4 pg</td>
<td>20.3 pg</td>
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<td>Serum LTC/D₄</td>
<td>86.7 pg</td>
<td>41.2 pg</td>
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<tr>
<td>Nasal PGE₂</td>
<td>98.3 pg</td>
<td>49.5 pg</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Serum PGE₂</td>
<td>85.9 pg</td>
<td>55 pg</td>
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<tr>
<td>Inspiratory ERM values</td>
<td>0.8</td>
<td>0.6</td>
<td>&lt; 0.05</td>
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<tr>
<td>Expiratory ERM values</td>
<td>0.8</td>
<td>0.6</td>
<td>&lt; 0.05</td>
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Table II

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<tr>
<td>Percent of eosinophil in biopsy</td>
<td>48.3%</td>
<td>18.7%</td>
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<td>Total eosinophil</td>
<td>571.4</td>
<td>351.2</td>
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<td>4.5</td>
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<td>Nasal PNL</td>
<td>9.2</td>
<td>9</td>
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<tr>
<td>Mast cell count in biopsy</td>
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<td>1.4</td>
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<td>103.1 pg</td>
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<tr>
<td>Serum PGE₂</td>
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<td>52.5 pg</td>
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<td>Inspiratory ERM values</td>
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<td>0.6</td>
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Table III

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<th>Fluticasone</th>
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<tr>
<td>Percent of eosinophil in biopsy</td>
<td>16.4%</td>
<td>29.7%</td>
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<td>Total eosinophil</td>
<td>115.4</td>
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<td>Nasal eosinophil</td>
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<td>4.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Nasal PNL</td>
<td>0.9</td>
<td>0.2</td>
<td>&gt; 0.05</td>
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<tr>
<td>Mast cell count in biopsy</td>
<td>4.8</td>
<td>5.6</td>
<td>&gt; 0.05</td>
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<tr>
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<td>25.09 pg</td>
<td>9.7 pg</td>
<td>&gt; 0.05</td>
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<td>Serum LTC/D₄</td>
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<td>23 pg</td>
<td>&gt; 0.05</td>
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<tr>
<td>Nasal PGE₂</td>
<td>48.8 pg</td>
<td>59.6 pg</td>
<td>&gt; 0.05</td>
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<td>Serum PGE₂</td>
<td>30.9 pg</td>
<td>47.2 pg</td>
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<tr>
<td>Inspiratory ERM values</td>
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<td>0.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Expiratory ERM values</td>
<td>0.2</td>
<td>0.1</td>
<td>&gt; 0.05</td>
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</table>

When we compared the effect of Cetirizine and FP on the evaluated parameters, FP was found to be significantly more effective than Cetirizine in decreasing the number of eosinophil in the nasal biopsy specimens, nasal smear and in the blood (p < 0.05) (table III).

DISCUSSION

Allergic rhinitis is a nasal inflammatory disease. After exposure to allergens, IgE activated mast cells in the nasal mucosa release mediators, like histamine, leukotrienes, prostaglandins and bradykinin. These mediators work independently or in combination to cause symptoms of nasal obstruction, rhinorrhea, sneezing and nasal itching. Inflammatory cells like eosinophils accumulate in the nasal mucosa, causing nasal symptoms and hyperresponsiveness to the allergen (6). In allergic rhinitis the symptoms occur with the interaction of released mediators, and neural and vascular structures in the nasal mucosa (7).

Histamine released by mast cells and basophils is an important mediator in the pathophysiology of allergic rhinitis. After immunologic provocation of mast cells and basophils they produce same symptomatic effect by histamine release which acts through H₁ receptors found in organs related with IgE mediated allergic reactions (8).

H₁ antihistamines and corticosteroids are used wide spread in the treatment of allergic rhinitis. H₁ antihistamines reduce the clinical expression of nasal itching, sneezing and rhinorrhea, but are relatively ineffective in the treatment of nasal obstruction. Corticosteroids inhibit all the symptoms including nasal obstruction (9).

Cetirizine, a hydroxyzine metabolite, is a second generation H₁ antagonist with high specificity to H₁ receptors, low metabolism level and H₁ receptor unrelated effects on the cells involved in the pathophysiology of allergy. It is also known that it has antiinflammatory effect by preventing migration of the inflammatory cells like eosinophils, neutrophiles and basophils to the IgE mediated allergic reaction area (10). Cetirizine is the second line H₁ antagonist which decrease the nasal congestion and also nasal obstruction.

Corticosteroids show antiinflammatory effect by decreasing capillary permeability and stabilizing the lysosomal membrane. They also decrease the late effects of allergic reactions by inhibiting the flow of arachidonic acid and blocking the effects of migration inhibitory factor (11). Because of the possible side effects they have to be used in minimal efficient the-
rapeutic dosage for a short period and if possible top-
ical preparations have to be used to decrease the risk of side effects and increase the therapeutic effects (12).

Nasal fluticasone propionate is an active, topical preparation. When the topical antiinflammatory activity of FP is compared with beclomethasone and triamcinolone acetonide it is 2 times and 9 times more effective, respectively. In appropriate dosage, systemic absorption of FP from the nasal mucosa is too low. Ratio of its local antiinflammatory effect to systemic activity is clearly high (13). For this reason FP is the choice of treatment in perennial allergic rhinitis (14).

Sheffer et al (15) and Rhioux et al (16) showed the Cetirizine treatment significantly decrease the eosi-
nophil count in tissue, nasal lavage fluid and systemic circulation. In this study percentage of eosinophils in biopsy, before and after treatment is 24.3 % and 7.9 % respectively (p < 0.05). In nasal smear mean eosinophil count decrease from 1.9 to 0.6 after treat-
ment (p < 0.05). Decrease in the mean total eosinop-
hil count from 468.2 to 352.3 is statistically signifi-
cant (p < 0.05).

Meltzer et al (17) and Bronsky et al (18), determin-
ed that there was significant decrease in the eosi-
nophil count in nasal mucosal biopsy material and na-
sal smear after FP treatment. In our study, mean eosinophil percentages in biopsy, eosinophil counts in nasal smear and total eosinophil counts have all decreased significantly. In addition, after treatment with FP and Cetirizine, mean decreases in eosinop-
hil counts in biopsy were 29.7 % and 16.4 %, in na-
sal eosinophil counts 4.2 and 1.4, and in total eosi-
nophil counts 220.2 and 115.9 respectively, and the differences between both treatments are statistically signifi-
cant (p < 0.05).

Simons et al (10) and Okayama et al (19) stated that Cetirizine shows its antiinflammatory effects by inhibi-
ting the mast cells besides the other cells. In accor-
dance with this date, in our study, mast cell count in the nasal mucosa biopsies were 6.3 and 1.5, before and after the treatment with Cetirizine respectively.

Juliusson et al (20) also determined that mast cell count in nasal mucosa decrease significantly after topical FP administration. In this study, mast cell in the nasal mucosa biopsies has decreased from 6.9 to
1.4, before and after FP treatment respectively. As a result, both drugs exhibit similar clinical results with different effects the mast cells.

The role of leukotrienes in immunology is known since 1930’s. Detection of leukotrienes in inflamma-
tory disease like asthma and allergic rhinitis has shown the pathogenesis and treatment goals of the
diseases (7).

LTC₄ and LTD₄ are derived from arachidonic acid with activation of 5-lipoxygenase enzyme. This enzyme is found in mast cells, basophils and eosinophils. Knani et al (21) stated that the levels of LTC₄ and D₄ in nasal secretions are higher in allergic rhinitis patients when compared with non-allergic patients.

Neclerio et al (22) stated that Cetirizine inhibits LTC₄ in vivo in early allergic reaction. In this study, in Cetirizine treated patients, LTC₄/D₄ level in nasal secretions were 45.4 pg and 20.3 pg before and after treatment, respectively. Mean serum LTC₄/D₄ value has decreased from 86.7 pg to 41.2 pg.

Fokken et al (23) stated that FP may also possibly decrease LTC₄/D₄ level. In this study, in the FP trea-
ted patients, LTC₄/D₄ levels in nasal secretion has de-
creased from the mean level of 44.7 pg to 35 pg, be-
fore and after treatment, respectively. This result is not statistically significant but the decrease in this level is well-compared with literature results. No sta-
tistically significant difference has been detected be-
 tween the pre and post treatment levels of serum LTC₄/D₄ and nasal LTC₄/D₄ (p > 0.05).

In this study, in Cetirizine treated patients, serum PGE₂ levels have decreased from 85.9 pg to 55 pg, nasal PGE₂ levels have decreased from 98.3 pg to 49.5 pg before and after treatment, respectively. These differences are statistically significant (p < 0.05). In the topical FP administered patients, mean serum PGE₂ levels have decreased from 99.8 pg to 52.6 pg, mean PGE₂ levels in nasal secretions have decreased from 103.1 pg to 43.5 pg after treatment (p < 0.05).

After Cetirizine treatment mean PGE₂ levels in plasma and nasal secretions decreased significantly. This finding was consistent with the data that Cetirizine had more potent antinflammatory effect compared with other antihistaminics. In the patients who are trea-
ted with Cetirizine or FP there no statistically signifi-
cant variation for the mean difference before and af-
ter treatment. This finding shows Cetirizine have antinflammatory effect similar to topical corticoste-
droids.

There was no statistically significant difference in the Cetirizine and FP administered patients according to the inspiratory and expiratory ERM levels in the pre and posttreatment periods (p > 0.05). This finding suggests that the both drugs decrease the nasal re-
sistance in similar levels. When the patients with allergic rhinitis administered Cetirizine and FP are compared, according to the eosinophil count in nasal smear, eosinophil percentage in biopsy of middle choncha anterior segment and total eosinophil count, FP was more effective than Cetirizine. However, ac-
cording to the parameters like serum and nasal LTC₄/D₄, mast cells, and ERM results there was no differences between these two drugs.
In conclusion, we think that FP and Cetirizine might be an alternative each other in selected patients in whom one of them cannot be administered because of possible side effects.

Palabras clave: Cetiricina. Proponato de fluticasona. Rinitis alérgica perenne.

RESUMEN

Fundamento: La rinitis alérgica es una reacción de hipersensibilidad de la mucosa nasal, mediada por IgE, y caracterizada por secreción, obstrucción y prurito nasal.

Pacientes y métodos: en este estudio se incluyeron 43 pacientes con rinitis alérgica perenne con el objetivo de comparar la eficacia de propionato de fluticasona (PF), un corticoide administrado en nebulización nasal, con cetiricina, un antihistamínico sistémico administrado por vía oral, que supuestamente carece de actividad antiinflamatoria no esteroide. A 22 pacientes se les administró cetiricina (10 mg/día en una sola dosis) durante 45 días. A los 21 pacientes restantes se aplicó PF (400 μg/día) 2 veces al día en cada ventana nasal durante 45 días.

Antes del tratamiento se efectuaron pruebas cutáneas a los pacientes. Antes y después del tratamiento se hicieron: recuentos de eosinófilos en sangre y frotis nasal; en suero y secreción nasal; en suero y frotis nasal; y además se realizó estudio electrornomomanométrico.

Además, antes y después del tratamiento, se evaluaron el porcentaje de eosinófilos y el recuento de mastocitos en las biopsias obtenidas a partir del borde anterior del cornete medio.

Resultados: cuando comparamos el recuento de eosinófilos en el frotis nasal, porcentaje de eosinófilos y recuento total de eosinófilos entre ambos grupos, se puso de manifiesto que PF fue más eficaz que cetiricina. Por otra parte, cuando comparamos el cociente LTC₄/LTD₄, en suero y frotis nasal, valores de PGE₂ y recuento de mastocitos y la resistencia de las vías respiratorias nasales determinadas mediante ERM, no se detectaron diferencias estadísticamente significativas entre ambos grupos.

Conclusión: los resultados del presente estudio demuestran que ambos fármacos pueden utilizarse alternativamente en caso de reacciones adversas a cualquiera de ellos.

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