MONTELUKAST EN RINITIS ALÉRGICA

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GRADO DE ACUERDO CON DISTINTAS AFIRMACIONES SOBRE EL ASMA: ALERGOLOGOS

<table>
<thead>
<tr>
<th></th>
<th>Muy+ Bastante de acuerdo</th>
<th>Ni de acuerdo, ni en desacuerdo</th>
<th>Muy+ Bastante en desacuerdo</th>
</tr>
</thead>
<tbody>
<tr>
<td>El FVE1, y el PEF a menudo tienen una escasa correlación con los síntomas</td>
<td>52</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Los pacientes cumplen mejor el tratamiento con comprimidos que con inhaladores</td>
<td>73</td>
<td>16</td>
<td>11</td>
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<td>Sería muy útil disponer de un agente que tratara tanto el asma como la RA</td>
<td>81</td>
<td>11</td>
<td>8</td>
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<tr>
<td>El uso de β₂ de larga duración puede producir tolerancia</td>
<td>71</td>
<td>19</td>
<td>11</td>
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<tr>
<td>Muchos pacientes no están controlados con el tratamiento</td>
<td>56</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>MK + ICS tiene un inicio de acción más rápido que doblar la dosis de ICS</td>
<td>69</td>
<td>17</td>
<td>13</td>
</tr>
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</table>
**ASOCIACION ENTRE RINITIS ALÉRGICA Y ASMA**

- Aproximadamente el 80% de los asmáticos presentan síntomas de rinitis alérgica

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**Prieto L, Gutierrez V, Morales C, Marin J. Differences in sensitivity, maximal response and position of the concentration-response curve to methacholine between asthmatics, patients with allergic rhinitis and healthy subjects. Respir Med. 1998 Jan;92(1):89-94.**

- The aim of this study was to detect differences in maximal response and position of the concentration-response curves to methacholine between asthmatics and subjects with allergic rhinitis. A total of 228 adults (107 mild asthmatics, 96 allergic rhinitic and 25 healthy control subjects) were challenged with methacholine. The test was interrupted when FEV1 dropped by more than 40% or when the highest concentration of methacholine (300 mg ml-1) had been administered. Concentration-response curves were characterized by their PC20 (concentration of methacholine that produced 20% fall in FEV1 = airway sensitivity), and if possible, by their EC50 (concentration of methacholine that produced 50% of the maximal response = position) and level of plateau. The proportion of subjects with plateau was significantly lower in asthmatics (18.7%) than in either allergic rhinitics (57.3%) or healthy subjects (92%). It was also significantly lower in allergic rhinitis than in healthy subjects. The level of plateau for asthmatics was (mean +/- SD) 33.5 +/- 5.3%, compared with 20.1 +/- 8.1% in allergic rhinitics and 13.7 +/- 6.7% in healthy subjects (P < 0.01). It was also higher in allergic rhinitics than in healthy subjects (P < 0.01). The EC50 values were decreased in asthmatics when they were compared with either allergic rhinitics or healthy subjects (geometric mean EC50 asthmatics = 2.7 mg ml-1, allergic rhinitics = 6.2 mg ml-1, healthy subjects = 8.7 mg ml-2, P < 0.001), but no significant differences were detected between allergic rhinitics and healthy subjects. These results demonstrate that in subjects with allergic rhinitis, the prevalence and level of the plateau on the methacholine concentration-response curve is intermediate between that of asthmatics and normals. Furthermore, while the asthmatic curves differ from normal in having both an increased maximal response and a leftward shift, the rhinitic curves differ only in terms of plateau level. These results suggest that airway responsiveness in asthma and allergic rhinitis may be a consequence of mechanisms that are at least partially different.
**SENSIBILIDAD A METACOLINA**

**ASMA vs RINITIS ALÉRGICA**

<table>
<thead>
<tr>
<th>PC20 (mg/ml)</th>
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<tbody>
<tr>
<td>300</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>0,1</td>
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<td>0,01</td>
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ASMA vs R. ALÉRGICA

SANOS

P<0.01


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We studied the role of atopy, as defined by positive skin tests to common inhalant allergens, in allergic bronchial inflammation. Endobronchial biopsies were taken via the fiberoptic bronchoscope in 13 symptomatic atopic asthmatics, 10 atopic nonasthmatics, and 7 normals. The numbers of mast cells, identified in the submucosa by immunohistochemistry using the AA1 monoclonal antibody against tryptase, were no different between the three groups, but electron microscopy showed that mast cell degranulation, although less marked in atopic nonasthmatics, was a feature of atopy in general. The numbers of eosinophils, identified by immunohistochemical staining using the monoclonal anti-eosinophil cationic protein antibody, EG2, were greatest in the asthmatics, low or absent in the normals and intermediate in the atopic nonasthmatics. In both atopic groups eosinophils showed ultrastructural features of degranulation. Measurements of subepithelial basement membrane thickness on electron micrographs showed that the collagen layer was thickest in the asthmatics, intermediate in the atopic nonasthmatics and thinnest in the normals. The results suggest that airways eosinophilia and degranulation of eosinophils and mast cells, as well as increased subepithelial collagen deposition, are a feature of atopy in general and suggest that the degree of change may determine the clinical expression of this immune disorder.
**INFLAMACIÓN BRONQUIAL**

**RINITIS ALÉRGICA**

<table>
<thead>
<tr>
<th></th>
<th>ASMA</th>
<th>RINITIS ALÉRGICA</th>
<th>SANOS</th>
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<tbody>
<tr>
<td>N=13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=10</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N=7</td>
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</table>

**Biopsia bronquial**


**MEMBRANA BASAL (m)**

- P<0.005
- P<0.005
- P<0.05

STUDY OBJECTIVES: To determine differences in exhaled nitric oxide (ENO) between subjects with allergic rhinitis with and without increased responsiveness to direct and indirect bronchoconstrictor agents. STUDY DESIGN: Cross-sectional study with the order of challenge tests randomized. SETTING: Specialist allergy unit in a university hospital. PATIENTS: Thirty-eight subjects without asthma with allergic rhinitis and 10 healthy nonatopic control subjects. MEASUREMENTS AND RESULTS: Participants were challenged with increasing concentrations of adenosine 5’-monophosphate (AMP) and methacholine. ENO was measured with the single-exhalation method. A positive response to both bronchoconstrictor agents was detected in nine subjects with allergic rhinitis, whereas four subjects showed increased responsiveness to AMP but not to methacholine. The geometric mean (range) ENO values were significantly higher in subjects with allergic rhinitis with increased responsiveness to either methacholine or AMP than in subjects with normal responsiveness to both agonists: 51.3 parts per billion (ppb) (22.0 to 108.5 ppb) vs 25.1 ppb (5.7 to 102.9 ppb, respectively) and healthy control subjects (11.2 ppb (5.0 to 31.9 ppb), p < 0.001). Subjects with allergic rhinitis with normal responsiveness to both agonists also had higher concentrations of ENO than healthy control subjects (p = 0.007). No correlation was found between ENO and either of the provocative concentrations of methacholine or AMP causing a 20% fall in FEV1. CONCLUSIONS: In subjects without asthma but with allergic rhinitis, the presence of bronchoconstriction in response to methacholine or AMP is associated with increased ENO concentrations. However, elevated concentrations of ENO are detected even in subjects with allergic rhinitis without airway hyperresponsiveness. These results suggest that the presence of airway hyperresponsiveness is not the only factor that determines the increased NO levels detected in subjects with allergic rhinitis.

BACKGROUND: Asthma and rhinitis often co-exist and there are data to suggest that they may be two ends of the same disease spectrum. Immunohistochemical studies have shown that eosinophilia in the airways is a feature of rhinitic patients without asthma. OBJECTIVE: The aim of our study was to examine whether cellular infiltration exists in the nasal mucosa of asthmatics even in the absence of symptoms and signs of rhinitis. METHODS: Nasal mucosa biopsies were taken from 27 non-atopic subjects and comprised nine asthmatic rhinitic patients (AR), eight asthmatic non-rhinitic patients (ANR) and 10 healthy control subjects (N). Bronchial mucosa biopsies were also taken simultaneously from some of the patients (n = 10) to determine whether there was an association between cellular infiltration in the nose and the lungs. The alkaline phosphatase-anti-alkaline phosphatase (APAAP) method was used on 6 micrometer thick cryostat sections using monoclonal antibodies against T cells (CD4, CD8), eosinophils (EG2) and mast cells (mast cell tryptase). Slides were counted blind and results expressed as cells per field. RESULTS: The results showed that eosinophil counts were higher in both asthma groups compared with control nasal biopsies (median values AR 8.3, ANR 9.2, N 2.1 cells per field, P < 0.01). Furthermore, there was a significant correlation between eosinophil cell counts in the nose and the airways (r = 0.851, P < 0.001). No differences in eosinophil numbers were detected between the two groups of asthmatics. Also, no differences were noted for any other cell type (i.e. CD4, CD8, tryptase) among the three study groups. CONCLUSIONS: These results show that eosinophil infiltration was present in the nasal mucosa of asthmatic patients even in the absence of rhinitis, and add further support to the hypothesis that asthma and rhinitis are clinical expressions of the same disease entity.
Allergic rhinitis and asthma often coexist and share a genetic background. Pathophysiologic connections between the nose and lungs are still not entirely understood. This study was undertaken to compare allergic inflammation and clinical findings in the upper and lower airways after segmental bronchial provocation (SBP) in nonasthmatic allergic rhinitis patients. Eight nonasthmatic, grass pollen-sensitive patients with allergic rhinitis and eight healthy controls were included. Bronchial biopsies and blood samples were taken before (T(0)) and 24 h (T(24)) after SBP. Nasal biopsies were obtained at T(0), 1 h after SBP (T(1)), and T(24). Immunohistochemical staining was performed for eosinophils (BMK13), interleukin (IL)-5, and eotaxin. The number of eosinophils increased in the challenged and unchallenged bronchial mucosa (p < 0.05) and in the blood (p = 0.03) of atopic subjects at T(24). We detected an increase of BMK13-positive and eotaxin-positive cells in the nasal lamina propria and enhanced expression of IL-5 in the nasal epithelium of atopic subjects only at T(24) (p < 0.05). SBP induced nasal and bronchial symptoms as well as reductions in pulmonary and nasal function in the allergic group. No significant changes could be observed in healthy controls. The study shows that SBP in nonasthmatic allergic rhinitis patients results in peripheral blood eosinophilia, and that SBP can induce allergic inflammation in the nose.
BACKGROUND: Allergic rhinitis (AR) and asthma are characterized by means of a similar inflammatory process in which eosinophils are important effector cells. The migration of eosinophils from the blood into the tissues is dependent on adhesion molecules.

OBJECTIVE: To analyze the aspects of nasobronchial cross-talk, we studied the expression of adhesion molecules in nasal and bronchial mucosa after nasal allergen provocation (NP).

METHODS: Nine nonasthmatic subjects with seasonal AR and 9 healthy control subjects underwent NP out of season. Bronchial and nasal biopsy specimens were taken before (T(0)) and 24 hours after NP (T(24)). Mucosal sections were analyzed for the presence of eosinophils, IL-5, eotaxin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and human endothelium (CD31).

RESULTS: At T(24), an influx of eosinophils was detected in nasal epithelium (P = .01) and lamina propria (P < .01), as well as in bronchial epithelium (P = .05) and lamina propria (P < .05), of the patients with AR. At T(24), increased expression of ICAM-1, as well as increased percentages of ICAM-1+, VCAM-1+, and E-selectin+ vessels, were seen in nasal and bronchial tissue of patients with AR. The number of mucosal eosinophils correlated with the local expression of ICAM-1, E-selectin, and VCAM-1 in patients with AR.

CONCLUSION: This study shows that NP in patients with AR results in generalized airway inflammation through upregulation of adhesion molecules.
BACKGROUND: Natural exposure to pollen provokes an increase in airway responsiveness in nonasthmatic subjects with seasonal allergic rhinitis. This natural exposure may induce inflammatory cell recruitment and cytokine release, leading to lower airway inflammation.

OBJECTIVE: The aim of this study was to characterize lower airway inflammation in nonasthmatic pollen-sensitive subjects.

METHODS: We performed immunohistochemical tests on bronchial biopsy specimens from subjects with rhinitis who had no past or current history of asthma to evaluate cytokine expression and inflammatory cell numbers and activation both in and out of the pollen season.

RESULTS: The number of CD4(+), CD8(+), and CD45RO(+) lymphocyte subpopulations were significantly higher during the pollen season compared with the out-of-season period (P < .04). Furthermore, EG1(+) cells tended to increase after natural pollen exposure (P = .06). The number of IL-5(+) cells increased significantly after natural exposure to pollen compared with out-of-season numbers (P < .01). This increase in IL-5 expression was correlated with the numbers of CD3(+), CD4(+), CD45RO(+), and EG1(+) cells. The numbers of tryptase-positive, IFN-gamma(+), and IL-4(+) cells did not change after natural exposure. CONCLUSION: This study showed that natural pollen exposure was associated with an increase in lymphocyte numbers, eosinophil recruitment, and IL-5 expression in the bronchial mucosa of nonasthmatic subjects with allergic rhinitis.
**STUDY OBJECTIVES:** To determine the effect of cessation of exposure to pollen on airway responsiveness to adenosine 5'-monophosphate (AMP) in subjects with pollen-induced rhinitis, and to explore the relationship between changes in airway responsiveness and changes in exhaled nitric oxide (ENO) levels.

**STUDY DESIGN:** Subjects were studied during the pollen season and out of season.

**SETTING:** Specialist allergy unit in a university hospital.

**PATIENTS:** Fourteen subjects without asthma with pollen-induced rhinitis who showed bronchoconstriction in response to methacholine and AMP during the pollen season and 10 healthy nonatopic control subjects.

**MEASUREMENTS AND RESULTS:** In subjects with pollen-induced rhinitis, ENO concentrations, provocative concentration of agonist causing a 20% fall in FEV₁ (PC(20)) methacholine, and PC(20) AMP were determined during the pollen season and out of season. Healthy control subjects were studied during the pollen season. In subjects with allergic rhinitis, PC(20) AMP increased from a geometric mean of 79.4 mg/mL (95% confidence interval [CI], 31.6 to 199.5 mg/mL) during the pollen season to 316.2 mg/mL (95% CI, 198.5 to 490.0 mg/mL) out of season (p < 0.004). The ENO concentrations decreased from 63.1 parts per billion (ppb) (95% CI, 50.1 to 79.4 ppb) during the pollen season to 30.2 ppb (95% CI, 23.4 to 38.0 ppb) out of season (p < 0.001). The ENO concentrations out of pollen season were still significantly increased in subjects with pollen-induced rhinitis when compared with healthy control subjects. There was no relationship between individual changes in ENO levels and changes in either PC(20) methacholine or PC(20) AMP.

**CONCLUSIONS:** In pollen-sensitive subjects with allergic rhinitis, the cessation of exposure to pollen is associated with a significant reduction of airway responsiveness to inhaled AMP. However, no association was found between allergen-induced changes in ENO values and in airway responsiveness to either direct or indirect bronchoconstrictors. These findings suggest that modifications in ENO and in airway responsiveness are the consequence of different alterations induced by allergen exposure on the lower airways.
RINITIS ALÉRGICA Y ASMA
POSIBLES MECANISMOS INTERACTIVOS

Aspiración de secreciones inflamatorias desde la VAS hacia los bronquios

Sustitución de respiración nasal por oral

Liberación de mediadores a circulación sistémica que alcanzan los bronquios

Reflejo naso-bronquial

Togias A. Allergy 1999;54(suppl 57):94-105.

SENSIBILIZACIÓN A ALERGENOS INHALADOS
ABORDAJE PARCELAR

EVITACIÓN ALERGENOS
MODULACIÓN RESP. TH₂
ANTAGONISTAS DE ILs
MONOCLONAL ANTÍgE
ANTAGONISTAS DE LTs
BACKGROUND: Histamine and cysteinyl leukotrienes seem to be important mediators of allergic rhinitis. OBJECTIVE: This multicenter, randomized, double-blind, parallel-group, placebo-controlled trial evaluated the effectiveness and tolerability of montelukast, loratadine, and combination therapy with montelukast and loratadine for treating patients with full seasonal allergic rhinitis. METHODS: After a 1-week, single-blind, placebo run-in period, 907 male and female patients aged 15 to 82 years were randomized to 1 of 4 treatments: montelukast 10 mg (n = 155), loratadine 10 mg (n = 301), combination montelukast 10 mg and loratadine 10 mg (n = 302), or placebo (n = 149), administered once daily at bedtime for 2 weeks. The primary endpoint was the daytime nasal symptom score (mean of congestion, rhinorrhea, pruritus, and sneezing). RESULTS: Mean symptom scores at baseline were similar for the four treatment groups. For each of the three active treatments, the difference was significant for the mean change from baseline compared with placebo (P < or = 0.001). However, the effect of montelukast/loratadine compared with loratadine alone, the primary comparison, was not significantly different. Differences for each therapy alone compared with placebo were also significant for most secondary endpoints, including nighttime symptom scores, eye symptoms scores, and rhinitis-specific quality of life. Differences for montelukast/loratadine compared with each therapy alone generally showed numerical superiority, and a few endpoints showed differences that were statistically significant. All active treatments showed a safety profile generally similar to placebo. CONCLUSIONS: Montelukast alone or in combination with loratadine is well tolerated and provides clinical and quality-of-life benefits for patients with seasonal allergic rhinitis.
EFICACIA DE MONTELUKAST
RINITIS ALÉRGIKA ESTACIONAL

Síntomas día

\[ \Delta \text{medio (±SE) desde basal} \]

- Placebo (n=149)
- Montelukast 10 mg (n=155)
- Loratadina 10 mg (n=301)
- Montelukast + loratadina (n=302)

\[ p < 0.001 \] *vs. placebo


EFICACIA DE MONTELUKAST
RINITIS ALÉRGIKA ESTACIONAL

Puntuación síntomas conjuntivales

\[ \Delta \text{medio desde basal} \]

- Placebo (n=148)
- Montelukast 10 mg (n=151)
- Loratadina 10 mg (n=299)
- Montelukast + loratadina (n=298)

\[ p < 0.001 \] *vs. placebo

BACKGROUND: Inhaled corticosteroids (ICS) affect many inflammatory pathways in asthma but have little impact on cysteinyl leukotrienes. This may partly explain persistent airway inflammation during chronic ICS treatment and failure to achieve adequate asthma control in some patients. This double blind, randomised, parallel group, non-inferiority, multicentre 16 week study compared the clinical benefits of adding montelukast to budesonide with doubling the budesonide dose in adults with asthma.

METHODS: After a 1 month single blind run in period, patients inadequately controlled on inhaled budesonide (800 microg/day) were randomised to receive montelukast 10 mg + inhaled budesonide 800 microg/day (n=448) or budesonide 1600 microg/day (n=441) for 12 weeks. RESULTS: Both groups showed progressive improvement in several measures of asthma control compared with baseline. Mean morning peak expiratory flow (AM PEF) improved similarly in the last 10 weeks of treatment compared with baseline in both the montelukast + budesonide group and in the double dose budesonide group (335 v. 30.1 l/min). During days 1-3 after start of treatment, the change in AM PEF from baseline was significantly greater in the montelukast + budesonide group than in the double dose budesonide group (20.1 v.9.6 l/min, p<0.001), indicating faster onset of action in the montelukast group. Both groups showed similar improvements with respect to "as needed" beta agonist use, mean daytime symptom score, nocturnal awakenings, exacerbations, asthma free days, peripheral eosinophil counts, and asthma specific quality of life. Both montelukast + budesonide and double dose budesonide were generally well tolerated. CONCLUSION: The addition of montelukast to inhaled budesonide is an effective and well tolerated alternative to doubling the dose of inhaled budesonide in adult asthma patients experiencing symptoms and inadequate control on budesonide alone.

**ESTUDIO COMPACT**

**DISEÑO DEL ESTUDIO**

<table>
<thead>
<tr>
<th>Período I</th>
<th>Período II</th>
</tr>
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<tbody>
<tr>
<td>Run-in (4 sem) Ciego-simple</td>
<td>Tratamiento activo (12 sem) Doble-ciego</td>
</tr>
<tr>
<td>Budesonida 400 µg cada 12 h</td>
<td>Montelukast 10 mg cada 24 h + Budesonida 400 µg cada 12 h</td>
</tr>
<tr>
<td></td>
<td>n=448</td>
</tr>
</tbody>
</table>

| | Budesonida 800 µg cada 12 h |
| | n=441 |

Semanas
Determinar si el tratamiento con montelukast asociado a budesonida proporcionaba beneficio adicional, comparado con budesonida sola, a los pacientes que presentaban concomitantemente asma y rinitis alérgica.

**Cambios desde basal (L/Min, LS Media ± SEM)**

- Montelukast (N=433)
- Budesonida (N=425)

Población global

**P=0.36**
Asma y Rinitis alérgica (AS/+RA)

Pacientes con asma y rinitis alérgica, definida por una historia positiva y un diagnóstico médico.

Asma sin Rinitis alérgica (AS/-RA)

Pacientes con asma sin una historia y un diagnóstico médico de rinitis alérgica.

ESTUDIO COMPACT
GRUPOS DE PACIENTES COMPARADOS

Población AS/+RA

Cambios desde basal (L/Min, LS Media ± SEM)

Montelukast (N=216)
Budesonida (N=184)

P<0.03
CONCLUSIONES

1. Las consecuencias de la sensibilización a los alergenos inhalados se observan en los diferentes órganos expuestos a los mismos.

2. El concepto “organicista” de la enfermedad alérgica es artificioso e irreal.

3. Diferentes estudios han demostrado la eficacia de montelukast en el tratamiento de las manifestaciones naso-oculares y pulmonares inducidas por la sensibilización a alergenos inhalados.

4. Resultados preliminares sugieren que montelukast es una buena opción para tratar conjuntamente todas las manifestaciones clínicas inducidas por la sensibilización a alergenos inhalados.