7. Clinical studies, metabolism and receptors

Controlled exposure to mite allergen for a dose-finding of dimethindene maleate (DMM)

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Abstract. The aim of the study was to develop a laboratory system to challenge mite allergic patients with physiological concentrations of Der p I in order to evaluate the efficacy of antiallergic drugs in mite allergic patients. A double-blind, placebo-controlled, cross-over study was designed with three consecutive sessions. Twelve patients with proven sensitivity to dust mite were treated with a single dose of dimethindene maleate in a FOAD formulation (4 and 8 mg vs. placebo) 12 h before a long-term challenge with mite allergen Der p I in the Vienna challenge chamber. Challenge was performed with a constant concentration of 40 ng Der p I per cubic meter of air for 4 h. Nasal parameters were recorded at 15 min intervals during long-term challenge. In comparison to placebo, dimethindene leads to a statistically significant reduction (p < 0.05) of the nasal response at both concentrations tested. The house-dust mite model in the Vienna challenge chamber thus proved to be a useful tool for drug investigations in mite allergies.

day

Materials and methods

Capsules containing 4 mg dimethindene as well as identically appearing placebo capsules were supplied by Zyma SA, Nyon and pieces of Dermatophagoïdes pteronyssinus were supplied by ALLERGON AB, Engelsholm Sweden.

The allergen provocation was carried out in the "Vienna Challenge Chamber" (VCC) [4] with air of constant humidity (30%), temperature (23 °C) and constant allergen load (40 ng Der p I/m³). At 5 min intervals, the air concentration of mite allergen was controlled by counting the airborne particles (4000/µm³). In parallel, a second sample was in use in order to quantify at hourly intervals the amount of Der p I allergen (40 ng Der p I/m³) by means of ELISA. The duration of provocation was 4 h.

The study followed a double-blind, placebo-controlled cross-over design. All patients were randomly assigned to the three treatment groups: either two capsules verum (in total 8 mg DMM), one capsule of verum and placebo (in total 4 mg DMM) or two capsules of placebo. A wash-out phase of 3 weeks was respected. Twelve hours after controlled drug application, the patients entered the challenge chamber. The nasal flow, the FEV₁, and the subjective symptoms were recorded every 15 min. The nasal secretion was gravimetrically measured every 30 min. At any time, adverse events were recorded.

The main criterion for efficacy was the change of nasal flow recorded at 150 Pa. Between group comparisons were carried out by means of ANOVA with alpha = 0.05. These AUC 0–240 min represent the total volume of obstructed air flow. Statistical comparison of objective data was done by means of cross-over analysis of variance and the Wilcoxon pairs test. All other criteria were just descriptively evaluated. The significance level required for rejection of the null hypothesis was alpha = 0.05.

Twelve patients (mean aged 25.9 ± 3.3 µ) took part in the study. House-dust mite sensitivity was proven by positive case history, positive skin prick test, RAST test and nasal provocation with house-dust mite allergen used in the VCC. None of the patients
Table 1. Effect of DMM and placebo on clinical parameters following allergen challenge.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>placebo</th>
<th>4 mg DMM</th>
<th>8 mg DMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline nasal flow at 150 Pa [cm²/sec]</td>
<td>878</td>
<td>773</td>
<td>774</td>
</tr>
<tr>
<td></td>
<td>174</td>
<td>181</td>
<td>146</td>
</tr>
<tr>
<td>Flow reduction after 240 min at 150 Pa</td>
<td>281</td>
<td>99</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>108</td>
<td>118</td>
</tr>
<tr>
<td>Auc 0–240 min of total flow, baseline corr.</td>
<td>875</td>
<td>395</td>
<td>284</td>
</tr>
<tr>
<td></td>
<td>339</td>
<td>384</td>
<td>310</td>
</tr>
<tr>
<td>VAS of overall status and subj. complaints</td>
<td>358</td>
<td>167</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>209</td>
<td>152</td>
<td>119</td>
</tr>
<tr>
<td>Total nasal secretion during 240 min (g)</td>
<td>6.8</td>
<td>1.5</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>9.2</td>
<td>2.8</td>
<td>3.4</td>
</tr>
</tbody>
</table>

ns no significant difference.
s significant difference (p<0.05) between verum and placebo (not inbetween verum).
s¹ significant difference (p<0.05) between 8 mg verum and placebo.
s² significant difference (p<0.05) between 4 mg verum and placebo.

Results

An overview of several parameters of interest is shown in Table 1. The development of the baseline adjusted total nasal flow at 150 Pa is demonstrated in Fig. 1. The FEV1 was not influenced by any treatment and remained stable within a normal range. No adverse event was observed during the study period (single dose administration).

Discussion

House-dust mite plays an essential role as an airborne allergen in perennial allergic rhinitis. A constant concentration of 40 ng Der p I per cubic meter of air leads to typical allergic symptoms in sensitized patients. The reaction pattern of the patients is similar to observations in pollen sensitized patients during a long-term pollen challenge in the VCC [5]. It is characterized by an instant nasal flow loss and symptom increase within the first 30 min followed by a plateau reaction for several hours. A sufficient antiallergic treatment is able to reduce the first (increase) phase, leading to a significant lower plateau reaction. Recent studies [6–8] demonstrated that some H1-receptor antagonists may also act as mast cell stabilizers, because of a measurable influence of the antihistamine on nasal obstruction which is mainly not histamine induced.

It is obvious from the data obtained that the higher dose of dimethindene tends to be slightly more effective than the lower one. However, the difference was not statistically significant. In contrast, the difference between both verum treatments and placebo was observed to be statistically significant at the p<0.05 level. This might be interpreted to mean that a capsule with 4 mg dimethindene is an adequate treatment for the usual disease conditions in most cases. It is of interest to note that both the subjectively perceived symptoms and their reduction by the dimethindene treatment, the measured nasal secretion, and the patient's overall judgment were consistent with the objective measurement of the nasal flow.

References


