Objective:
The Vienna Challenge Chamber (VCC) is an established method for the controlled exposure of patients to specific allergens, used to make valid comparisons between antihistamines. The aim of the two placebo-controlled, randomised studies reported here was to compare the efficacy and safety of levocetirizine 5 mg od and loratadine 10 mg od in subjects suffering from seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR).

Subjects and methods: During each study period, SAR and PAR subjects were exposed to grass pollen or house-dust mite allergens, respectively for 6 h on 2 consecutive days in the VCC. Each day, medications were administered 2 h after the start of the challenge; with a washout of at least 5 days between each period. The main criterion for evaluation of efficacy was the major symptom complex (MSC) for SAR and the complex symptom score (CSS) for PAR.

Results: The pattern of patients’ response was similar in SAR and PAR. Both levocetirizine and loratadine were superior to placebo in alleviating SAR and PAR symptoms at all time intervals evaluated during the two study days. Levocetirizine decreased the mean MSC score significantly more than loratadine at all time intervals in SAR subjects, with the most marked difference observed on day 2 ($p = 0.002$). In PAR patients, although with borderline significance ($p = 0.08$), levocetirizine decreased the mean CSS more than loratadine. Levocetirizine appeared to have a faster onset of action than loratadine in SAR (45 min versus 1 h 15 min) and PAR (1 h versus 1 h 30 min). However, these apparent differences were not tested for statistical significance. Both medications were well tolerated and no treatment-related adverse events were reported. This level of antihistamine efficacy was maintained regardless of whether the subjects’ rhinitis was seasonal or perennial.

Conclusion: This study demonstrated that levocetirizine is superior to loratadine in improving symptoms in SAR and that there is a similar trend in PAR.

SUMMARY

A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit – the Vienna Challenge Chamber (VCC)

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Key words: Grass pollen – House dust mite – Levocetirizine – Loratadine – Perennial allergic rhinitis (PAR) – Seasonal allergic rhinitis (SAR) – Vienna Challenge Chamber
Introduction

Allergic rhinitis is a common condition affecting a large percentage of the population; estimates of the prevalence range from 9 to as high as 42%\(^1,^2\). It can be classified as seasonal (SAR) or perennial (PAR) depending on whether symptoms are manifested at defined yearly intervals or throughout the year, respectively. Second generation antihistamines (\(\text{H}_1\)-antagonists) are the mainstay of treatment for both SAR and PAR, effectively relieving symptoms such as sneezing, pruritus and rhinorrhea\(^3,^4\).

The evaluation and comparison of antihistamines in the treatment of allergic rhinitis is often confounded by limitations in the study methodology. Traditional outpatient studies, involving environmental exposure of subjects to specific allergens, can provide valuable information with regard to the effectiveness of a treatment, as they closely resemble real-life situations. However, these studies can be subject to large variability in the concentration of allergen and hence extreme fluctuation in the levels that a subject is exposed to. For example, pollen concentrations can vary from region-to-region, from year-to-year, within a season and even within a day between 0 and 20,000 grains/m\(^3\) of air; low pollen counts and other environmental factors can lead to the reporting of false-negative results. Similarly, the room concentration of airborne house-dust mite (HDM) allergens, responsible for the symptoms of PAR\(^5\), can vary from 0.03 to more than 30 ng/m\(^3\). The consistent recording of results over a period of several days in outpatient studies represents a further problem for investigators; patient compliance in the accurate documentation of symptoms in study diaries decreases with each study day. Consecutive objective measurements are difficult to produce. Therefore, large subject numbers and long observation periods are often required to obtain any meaningful results.

The Vienna Challenge Chamber (VCC) has been developed to overcome the problems associated with field-based studies\(^6\). It is a standardised method that enables simultaneous allergen challenge of up to 20 subjects under controlled and reproducible conditions for several hours at a time. The VCC has been validated against traditional tests including: ocular challenge tests (OCT), nasal challenge tests (NCT) and the environmental challenge situation (ECS)\(^7,^8\). Generally, comparable results are found between all tests, however, the data obtained from the VCC are more precise and reproducible as determined after several pollen and HDM allergen challenges. Thus, the VCC has become a standard method for comparing antihistamines in the treatment of SAR and PAR. Up to now it has never been investigated whether individual antihistamines differ in terms of their onset, efficacy and duration of action in patients with SAR and PAR, respectively. The standardized allergen challenge model of the VCC, providing reproducible and consistent results, should make this possible.

Previous studies in the VCC have demonstrated the effectiveness of cetirizine, a potent antihistamine, in reducing symptom severity in allergic rhinitis. Both cetirizine (10 mg) and fexofenadine (120 mg) significantly reduced nasal symptoms in subjects with SAR, although cetirizine demonstrated a longer duration of action than fexofenadine and controlled symptoms better at 22–24 h post dose\(^9\). Another study evaluated the effects of cetirizine in PAR using the VCC. An oral cetirizine (5 mg) formulation with sustained-release pseudoephedrine (120 mg) relieved nasal congestion and other objective and subjective symptoms to a significantly greater extent than placebo in subjects challenged with HDM\(^10\). Loratadine, a second-generation antihistamine with a prolonged duration of action, also reduces symptom severity in subjects with SAR as determined in the VCC\(^11,^12\). Loratadine and cetirizine have recently been compared in an environmental exposure unit, similar to the VCC. Cetirizine had an earlier onset of action compared with loratadine and was more effective in reducing the Total Symptom Complex (TSC) and Major Symptom Complex (MSC) scores\(^13\).

Cetirizine is the (R)-enantiomer of cetirizine, which has been shown to be responsible for the clinical efficacy of the racemate\(^14,^15\). A recent randomised, double-blind study demonstrated that levocetirizine (2.5, 5 and 10 mg), once-daily for 2 weeks, significantly reduced symptom severity in subjects with SAR, with respect to placebo\(^16\). However, its effectiveness in allergic rhinitis has not been assessed in the controlled environment of the VCC. The reported studies here aimed to distinguish the efficacy and safety of levocetirizine and loratadine in the VCC in two populations of subjects, one with confirmed SAR and the second with confirmed PAR, challenged with grass pollen or HDM, respectively.

Patients and methods

Study Design

Two studies, one in SAR patients and one in PAR patients, were performed according to comparable protocols. These investigations were randomised, placebo-controlled, double-blind trials employing a three-way cross-over design to compare the efficacy and safety of levocetirizine and loratadine, given for 2 consecutive days, in reducing the symptoms of SAR or PAR in subjects sensitised to grass-pollen or HDM, respectively, in the VCC over a 6-h period. Studies
lasted at least 16 days, consisting of three treatment periods of 2 consecutive days followed by at least 5 wash-out days after the first and second period. On days 1 and 2 of each treatment period, the eligibility of each subject was confirmed; heart rate and blood pressure were measured; and objective and subjective symptoms of SAR or PAR were evaluated before entering the VCC.

Both studies were conducted in accordance with Good Clinical Practice Guidelines (International Conference on Harmonisation) and the Declaration of Helsinki (last revised in South Africa, October 1996). They were approved by the Ethics Committee of the University of Vienna.

Study Population

Informed consent was obtained from each subject before entry into the study. Subjects were males and females of 19–55 years of age who had suffered, for at least 2 years, from SAR due to grass pollen or PAR due to HDM as documented in the subject’s history, and with such severity that it required pharmacological intervention each year. All subjects had to have positive Radio-Allergo Sorbent Test (RAST ≥ class 2) and/or positive skin-prick tests (SPT ≥ 4 mm diameter) performed within the last year for grass pollen or HDM allergens. If test results were not available, a SPT had to be performed at the selection visit. Female subjects were either without childbearing potential or those who followed a medically acceptable contraceptive method; lactating or pregnant women were excluded. The Major Symptom Complex (MSC) score on day 1 in each period before entering the VCC had to be ≤ 4 for SAR subjects and the Complex Symptom Score (CSS) had to be ≤ 3 for PAR subjects.

Subjects were excluded from the studies if they had known alcohol or drug addiction; known intolerance to levocetirizine, other piperazines or loratadine; known allergy to lactose, cellulose or corn starch; presence of significant nasal deformities leading to >50% obstruction; symptomatic bronchial asthma; or ear, nose or throat infection within 30 days of the study start. Also excluded were subjects who had used other medications to treat allergies at intervals prior to the study start, which were predetermined to be unacceptable.

Study Medications

Each subject in either the SAR or PAR study was randomised to one of three treatment sequences. The dosage schedule was identical for each of the three treatment periods; subjects received one 5 mg levocetirizine tablet, one 10 mg loratadine tablet or one placebo tablet orally according to their treatment sequence. Study medications were administered 2 h after the beginning of exposure to allergens in the VCC (maximum of symptoms) on days 1 and 2 of each treatment period (Figure 1).

The Vienna Challenge Chamber

All efficacy and safety variables were assessed during allergen challenge in the VCC. Up to 14 subjects were
challenged at any one time and all subjects were under constant supervision by staff who remained outside of the chamber. The VCC was charged with cleaned and dried indoor air loaded with a qualitatively and quantitatively determined concentration of allergen. Subjects with SAR were exposed to grass pollen concentrations of 1500 grains/m$^3$ air. Subjects with PAR were challenged with HDM faeces, at a stable concentration of 1000 particles/m$^3$ air. Allergens were dispensed over a period of 6 h during the 2 consecutive days by an automatic supply unit into a constant turbulent flow of air. Allergen concentration and chamber humidity were monitored every 5 min, maintaining a temperature of 24–26°C and humidity of 30–35%.

Main Outcome Measures

For the purpose of the analysis, four time intervals were considered (Figure 1).

Efficacy and Safety Measurements

Subjective assessment of symptoms was made before the subject entered the VCC and then every 15 min during the 6 h of exposure to allergen. After leaving the VCC, assessments were made every 2 h for a further 8 h on the first day of the study period. Runny and itchy nose, sneezing, watery and itchy eyes, and nasal obstruction were scored on a five-point scale. The subject’s global evaluation of satisfaction was recorded on a 100 mm visual analogue scale (VAS). Objective assessments included: nasal congestion, measured by anterior rhinomanometry; nasal secretions by weighing handkerchiefs; and in subjects with PAR, pulmonary function tests, before allergen exposure in the VCC and every 30 min during exposure on days 1 and 2.

Primary Efficacy Variable

The main criteria to evaluate efficacy was the MSC score in subjects with SAR and the CSS in those with PAR. The primary efficacy variable was the mean MSC or CSS change from baseline over time-interval 1. MSC was defined as the sum of scores for runny nose, itchy nose, sneezing, watery eyes and itchy eyes, and CSS as the sum of runny nose, itchy nose and sneezing.

Secondary Efficacy Variables

Secondary efficacy variables included: the change from MSC score or CSS at baseline over time-intervals 2–4; the change in MSC or CSS plus nasal obstruction score from baseline over all time intervals; and the intensity of response, defined as the percentage reduction in the change from baseline score in the mean MSC score or CSS over all time intervals.

Exploratory Variables

Exploratory variables included: the change from baseline in the mean individual symptom score over all time intervals; the nasal congestion measured by anterior rhinomanometry; the subjects global evaluation of satisfaction, assessed by VAS; the amount of nasal secretion measured by weighing handkerchiefs; and the onset of action of each active treatment.

Sample Size

Seventy-two SAR subjects were required to detect, with a power of 80% and, using a 5% one-sided test, an effect size of 0.42 in MSC over time-interval 1. Thirty-six PAR subjects were required to detect, with a power of 90% and using a 5% two-sided test, a difference of 2.5 CSS units, assuming a common standard deviation of 2.5 score units.

Randomisation and Blinding

The assignment of subjects to a treatment sequence was performed according to a randomisation list prepared by computer using a complete set of $3 \times 3$ Latin squares. Treatments were administered in a double-blind manner by placing the tablets of levocetirizine, loratadine and placebo into capsules with an identical shape, size, taste and colour.

Statistical Methods

The populations for which analyses were conducted were the intention-to-treat population (ITT) and the per-protocol population (PP). The primary efficacy variable in subjects with SAR and PAR was analysed using a linear mixed model. The fixed factors were the treatment period and the treatment. The subject was considered to be a random effect and the baseline score was added as a co-variate. No carry-over effect was anticipated due to the presence of a sufficient wash-out time between treatment periods. For the analyses related to the MSC, levocetirizine and loratadine were compared using a one-sided test ($p = 0.05$). The upper limit of the 90% confidence interval of the difference in least-square means for the comparison between levocetirizine and loratadine was provided with the associated $p$-value. For subjects with PAR, the global null hypothesis of equality was tested between the three treatment groups. The treatment difference was estimated in a pairwise fashion by the difference in the least-square means with its associated 95% confidence
Change from baseline MSC score or CSS at time-interval 1 (4 h after administration of medications): the ITT population in each subject group represents those subjects who received at least one dose of study medication (Table 2). Following treatment with levocetirizine and loratadine, the mean MSC score and the CSS were evaluated.

### Results

A total of 73 and 39 subjects with SAR and PAR, respectively, were randomised to receive the study treatment (Figure 2). Sixty-eight to seventy-one SAR subjects and 35 –37 PAR subjects during the various treatment periods were evaluable.

### Demographic Data

Duration of SAR/PAR was similar between those subjects suffering from SAR or PAR (Table 1). All subjects suffering from SAR or PAR were positive for allergy to grass pollen and all those with PAR were positive for house-dust mites as determined by SPT or RAST (Table 1).

### Table 1. Duration and diagnosis of SAR and PAR

<table>
<thead>
<tr>
<th>Duration of SAR/PAR (years)</th>
<th>Skin prick test</th>
<th>Diagnosis of SAR/PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ND†</td>
<td>++</td>
</tr>
<tr>
<td>SAR</td>
<td>12.6</td>
<td>55</td>
</tr>
<tr>
<td>PAR</td>
<td>12.3</td>
<td>4</td>
</tr>
</tbody>
</table>

| SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; RAST = Radio-allergo Sorbent Test; ND = not determined
| Class 1 = doubtful; classes 2–3 = positive; class ≥ 4 = very positive
| ND: RAST test only performed
| †ND: Skin prick test only performed

Secondary efficacy variables in subjects with SAR were analysed as for the primary efficacy variable, while those for subjects with PAR were analysed in a descriptive way. A 95% confidence interval and a p-value associated with a two-sided test (p = 0.05) of the least square means was provided for all other comparisons. Exploratory variables were analysed in a similar manner to the primary efficacy variable except that a two-sided 95% confidence interval was provided for all pairwise comparisons.
significantly decreased compared with placebo during the 4 h post study-medicintake (Table 2). In subjects with SAR, the difference in adjusted means versus placebo was −3.26 and −2.40 for levocetirizine and loratadine, respectively (p < 0.001; Table 2). In addition, levocetirizine decreased the mean MSC score to a highly significant greater extent than loratadine during time-interval 1 in subjects with SAR; the difference in adjusted means between levocetirizine and loratadine was −0.86 (p = 0.007; Table 2). In subjects with PAR, the difference in adjusted means versus placebo was somewhat smaller but still highly significant for both medications: −1.61 for levocetirizine and −1.16 for loratadine (p < 0.001; Table 2). There was again a trend for a better improvement of CSS in PAR subjects treated with levocetirizine as compared to loratadine although the numerical superiority did not reach significance during the first 4 h of treatment (p = 0.08; Table 2).

Secondary Efficacy Variables

Change from Baseline MSC Score or CSS at Time-intervals 2–4

The overall treatment effect of levocetirizine and loratadine was highly significant versus placebo in subjects with SAR or PAR (p < 0.001).

In subjects with SAR, the improvement in mean MSC score at time intervals 2–4 (Table 3; Figures 3 and 4) was consistently and statistically significantly greater after treatment with levocetirizine as compared to loratadine (p = 0.042, 0.02 and 0.002 for time intervals 2, 3 and 4 respectively). The fact that, on day 2, prior to the second medication exposure (time-interval 3), levocetirizine improved significantly the mean MSC score compared with both loratadine and placebo suggests that the effect of levocetirizine treatment persists longer than that of loratadine (p = 0.02). The

Figure 2. Patient disposition in a clinical trial comparing levocetirizine and loratadine in subjects with Seasonal Allergic Rhinitis (SAR) or Perennial Allergic Rhinitis (PAR) exposed to grass pollen or house-dust mite allergens, respectively, in the Vienna Challenge Chamber
**Table 2.** Change from baseline MSC score or CSS over time-interval 1 in subjects with SAR and PAR (ITT population) a negative adjusted mean shows an improvement

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>During treatment (change from baseline)</th>
<th></th>
<th></th>
<th>Difference in adjusted mean versus loratadine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>Adjusted mean (SE)</td>
<td>Difference in adjusted mean versus placebo</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td><strong>SAR (MSC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levo</td>
<td>70</td>
<td>11.54 (2.85)</td>
<td>-5.19 (0.29)</td>
<td>-3.26</td>
<td>-3.94, -2.57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lorat</td>
<td>71</td>
<td>11.06 (2.83)</td>
<td>-4.33 (0.29)</td>
<td>-2.40</td>
<td>-3.08, -1.72</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>69</td>
<td>11.20 (2.70)</td>
<td>-1.94 (0.29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PAR (CSS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levo</td>
<td>38</td>
<td>8.4 (1.7)</td>
<td>-3.36 (0.31)</td>
<td>-1.61</td>
<td>-1.10, -2.11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lorat</td>
<td>37</td>
<td>8.5 (2.0)</td>
<td>-2.92 (0.31)</td>
<td>-1.16</td>
<td>-0.66, -1.66</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>37</td>
<td>8.5 (1.7)</td>
<td>-1.76 (0.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MSC = Major Symptom Complex Score; CSS = Complex Symptom Score; SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; CI = confidence interval; Levo = 5 mg levocetirizine; Lorat = 10 mg loratadine

**Table 3.** Change from baseline in Major Symptom Complex score over time-intervals 2–4 in subjects with SAR (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>During treatment (change from baseline)</th>
<th></th>
<th></th>
<th>Difference in adjusted mean versus loratadine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>Adjusted mean (SE)</td>
<td>Difference in adjusted mean versus placebo</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td><strong>Time-interval 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levocetirizine 5 mg</td>
<td>69</td>
<td>11.48 (2.82)</td>
<td>-8.56 (0.33)</td>
<td>-3.14</td>
<td>-3.87, -2.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Loratadine 10 mg</td>
<td>70</td>
<td>11.01 (2.83)</td>
<td>-7.92 (0.33)</td>
<td>-2.50</td>
<td>-3.23, -1.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>68</td>
<td>11.19 (2.72)</td>
<td>-5.42 (0.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time-interval 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levocetirizine 5 mg</td>
<td>70</td>
<td>11.54 (2.85)</td>
<td>-4.10 (0.34)</td>
<td>-2.79</td>
<td>-3.47, -2.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Loratadine 10 mg</td>
<td>70</td>
<td>11.01 (2.83)</td>
<td>-3.39 (0.34)</td>
<td>-2.08</td>
<td>-2.76, -1.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>68</td>
<td>11.19 (2.72)</td>
<td>-1.31 (0.34)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Time-interval 4</strong></td>
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</tr>
<tr>
<td>Levocetirizine 5 mg</td>
<td>70</td>
<td>11.54 (2.85)</td>
<td>-5.41 (0.35)</td>
<td>-3.95</td>
<td>-4.70, -3.21</td>
<td>&lt; 0.001</td>
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<tr>
<td>Loratadine 10 mg</td>
<td>70</td>
<td>11.01 (2.83)</td>
<td>-4.30 (0.35)</td>
<td>-2.84</td>
<td>-3.58, -2.10</td>
<td>&lt; 0.001</td>
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<tr>
<td>Placebo</td>
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<td>11.19 (2.72)</td>
<td>-1.46 (0.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
most marked difference between treatment groups in SAR was observed at time-interval 4, when subjects were exposed to allergens a second time. The superiority of levocetirizine over loratadine was demonstrated by a MSC score change from baseline of $-1.11$ ($p = 0.002$; Table 3).

In subjects with PAR, both levocetirizine and loratadine showed a significant improvement in the change from baseline CSS over time-intervals 2–4 (Figures 3 and 4). The largest difference in adjusted means versus placebo was observed at time-interval 4 (1.94 and 1.53 for levocetirizine and loratadine,
respectively, \( p < 0.001 \)). Although there was a trend for CSS scores to be numerically superior in the levocetirizine versus the loratadine group, this difference could not reach statistical significance.

Intensity of response: over time-interval 1 more subjects receiving the active treatments had a larger percentage reduction in MSC score or CSS from the baseline when compared with the placebo group. A similar trend was also observed when comparing levocetirizine to loratadine in subjects with SAR. At time-interval 1, 90% of SAR subjects in the levocetirizine group had a percentage reduction of at least 20% compared with 78.9 and 42% for loratadine and placebo, respectively (Figure 5). The number of 50% responders over time-interval 1 was also larger for levocetirizine compared with loratadine and placebo in SAR (44.3, 35.2 and 7.2%, respectively).

A similar trend was observed in subjects with PAR: 83.8% of the subjects receiving levocetirizine had an improvement of at least 20% in the CSS score compared with 66.7% of subjects in the loratadine group and 43.2% in the placebo group (Figure 5).

### MSC/CSS Plus Nasal Obstruction Scores

Compared with the MSC scores and CSS, as determined in the primary efficacy analysis, the MSC/CSS plus nasal obstruction scores decreased in a similar manner in response to active treatment. In subjects with SAR, the difference in adjusted means was significantly in favour of levocetirizine over loratadine at time intervals 1 \((-1.00, p = 0.007)\), 3 \((-0.79, p = 0.026)\) and 4 \((-1.31, p = 0.002)\). In subjects with PAR, levocetirizine and loratadine mediated a significant improvement in the change from baseline of CSS plus nasal obstruction score over time-interval 1 (adjusted means versus placebo 1.81 and 1.33, respectively, \( p < 0.001 \)). Similar results were obtained at all time-intervals analysed. The difference between levocetirizine and loratadine in the PAR subjects at time-interval 1 reached borderline significance in favour of levocetirizine (adjusted mean versus loratadine 0.48, \( p = 0.099 \)).

### Nasal Obstruction Scores

Nasal obstruction score (not part of the MSC) was assessed as a subjective evaluation. The baseline score was similar to the baseline scores for runny and itchy nose. However, the magnitude of the changes from baseline was not as large as for these symptoms. Levocetirizine demonstrated a slightly greater reduction over time-intervals 1, 3 and 4. The largest trend in favour of Levocetirizine occurred during time-interval 4. This latter fact was also observed for the runny nose, itchy nose and sneezing symptoms.

### Exploratory Variables

Nasal airflow and secretions: in subjects with SAR, there were no differences between active treatments in nasal
flow, as measured by anterior rhinomanometry, over time-interval 1. Both levocetirizine and loratadine were significantly more active than placebo (adjusted means versus placebo: 42.3 cm/s, \( p = 0.041 \) for levocetirizine and 61.2 cm/s, \( p = 0.003 \) for loratadine). However, at time-intervals 3 and 4 only levocetirizine demonstrated a significant difference over placebo in the improvement of nasal airflow. A significantly better effect on nasal airflow of levocetirizine over loratadine was observed at time-interval 4 in subjects with SAR; the difference in adjusted means versus loratadine was 55.9 cm/s (\( p = 0.004 \)). Although a similar trend was observed in subjects with PAR, neither levocetirizine nor loratadine reached statistically significant effects on nasal airflow, measured by anterior rhinomanometry or PNIF.

Levocetirizine was consistently better than placebo and loratadine in reducing nasal secretions in subjects with SAR. It was significantly superior to loratadine in improving these symptoms at time-intervals 1 and 3, with differences in adjusted means of \(-0.44 (p = 0.011)\) and \(-0.40 (p = 0.017)\), respectively. Both levocetirizine and loratadine decreased nasal secretions in subjects with PAR compared with placebo (\( p < 0.001 \)). However, no differences were observed between active treatments in these subjects at any time interval studied.

Global Evaluation of Subject Satisfaction

Compared with placebo, and at any time interval, both active treatments demonstrated a significant improvement from baseline in the global evaluation of subject satisfaction (\( p < 0.001 \)), assessed on a 100 mm VAS, in subjects with SAR. Satisfaction scores in the levocetirizine group were consistently higher than those in the loratadine group, however, the difference did not reach statistical significance. Results in the PAR subjects were similar but with generally smaller differences between the groups.

Onset of Action

Onset of action was defined as the first time-point after which the study medications demonstrated a significant difference over placebo in change from baseline MSC score or CSS. Levocetirizine had a faster onset of action than loratadine in both SAR and PAR. The treatment effect of levocetirizine was observed already at 45 min (\( p = 0.050 \) versus placebo) and 1 h (\( p < 0.005 \) versus placebo) after medication intake in subjects with SAR or PAR, respectively, compared with 1 h 15 min (\( p < 0.001 \) versus placebo) or 1 h 30 min (\( p = 0.043 \) versus placebo) for loratadine.

Adverse Events

Over the three study periods, adverse events were reported in six SAR subjects and three PAR subjects. None of the adverse events were serious and none were considered to be related to study medication. There were no differences in safety between the treatment groups.

Discussion

Among subjects with confirmed SAR or PAR who underwent controlled challenge with grass pollen or HDM over 2 consecutive days in the VCC, the antihistamines levocetirizine and loratadine reduced the severity of signs and symptoms at all time intervals, as measured by the MSC score and the CSS (± nasal obstruction scores), compared with placebo.

The type of disease (e.g. SAR or PAR) had no influence on the onset of action of the 2 antihistamines. Four hours after drug intake the efficacy (symptom reduction) in the active treated SAR patients was about 57% (placebo 20%), in the active treated PAR patients 50% (placebo 23%). Twenty-four hours after drug intake the difference in symptom score between active treated and placebo patients was still 50% in SAR patients and 63% in PAR patients, respectively (compared to the efficacy 4 h after drug intake).

In subjects with SAR, levocetirizine improved the MSC score significantly more than loratadine at all time intervals evaluated. Significant differences in favour of levocetirizine were also observed for individual symptom scores at different time intervals. Interestingly, levocetirizine’s superiority over loratadine increased progressively from time-interval 1 through to time intervals 3 and 4. That may imply that with the longer term treatment the differences between the medications could be more pronounced. This is supported by the overall intensity of response scores in MSC, which revealed that 90% of the SAR subjects treated with levocetirizine achieved a reduction in their MSC score of > 20%. Control of individual signs and symptoms was also in favour of levocetirizine. Sneezing, runny and itchy nose, during treatment interval 4, all scored significantly better in the levocetirizine than in the loratadine group (\( p < 0.05 \)). In addition, MSC scores during time-interval 3, which reveals the duration of activity, were significantly better in the subjects treated with levocetirizine (\( p < 0.05 \) vs loratadine). This was true even when nasal obstruction was included in the symptom score.

Not only was there a difference between the two treatment groups in the duration of action but a
significant difference was also observed in the onset of action. Patients with annoying allergic SAR need their symptoms controlled as quickly as possible. The SAR subjects in this study felt symptom relief only 45 min after levocetirizine intake. This is remarkable when compared not only to the slower onset of action of loratadine (75 min) in this study but also when compared to other studies performed in the same or similar controlled environments. Generally, the onset of action expected with common antihistamines is 1–3 h after medication intake. For example, two VCC studies performed with desloratadine (the active metabolite of loratadine) reported an onset of action of 75 and 105 min. In another environmental exposure unit, loratadine was reported to have an onset of action of 3 h. Studies in healthy volunteers with astemizole and terfenadine forte reported an onset of action of 107 and 153 min, respectively.

Nasal obstruction, a symptom which has recently attracted attention with the newer generation antihistamines was also studied in the present study and levocetirizine showed a consistent improvement over placebo with \( p < 0.001 \) throughout all the treatment intervals (\( p = 0.003 \) only at interval 3). Loratadine also exhibited a significant improvement of nasal obstruction over placebo, however, its effect was consistently inferior to that of levocetirizine. This was also true of improvement in nasal airflow measured by anterior rhinomanometry; levocetirizine was superior to loratadine at time-interval 4, while the effect of loratadine was comparable with placebo at this point.

In subjects with PAR, a similar trend of superiority for levocetirizine over loratadine was observed at all time intervals, particularly time-interval 1, although the differences between the two active treatments were not statistically significant. It should be noted that the PAR study was powered to detect a difference only between the treatment groups and placebo but not between the two active treatments (see sample size section). Since PAR symptoms are subtler than the symptoms in SAR, more subjects would be needed to detect a statistical and clinically significant difference between two antihistamines. Taking into consideration the constrictions of the VCC study methodology (up to 20 subjects can be challenged at any time point), the number of subjects participating in the PAR trial was smaller as compared with the SAR study (\( n = 39 \) versus 73).

The present investigation also found that the superior efficacy of levocetirizine over loratadine in SAR increased over time; the superiority of levocetirizine in various measures was more pronounced at time-interval 4, following the second medication administration on day 2. This is an important finding that proves not only the longer-lasting but also the more consistent effect of levocetirizine.

One of the major and most troublesome symptoms of allergic rhinitis is a reduction in nasal patency and so measurements of nasal airflow are a good indication of treatment efficacy. It is interesting to note that at time-intervals 3 and 4 loratadine did not exhibit any difference from placebo with regard to effects on nasal airflow, as measured by anterior rhinomanometry. Other studies in the VCC that used nasal airflow as an efficacy parameter reported the effects of the loratadine metabolite desloratadine over a period of up to 360 min (6 h). However, no studies so far have used 22–24 h as an efficacy time-point. Thus, this is the first study reporting a difference in the duration of action between antihistamines, with levocetirizine exhibiting a much longer and more potent efficacy than loratadine. It would be interesting to compare the duration and potency of action of desloratadine and levocetirizine in a similar 24-h duration study.

In addition, at time-interval 4, a significant difference in the global evaluation of subject satisfaction between levocetirizine and loratadine was recorded in subjects with SAR. This coincides with significant improvements in the subjective symptoms of runny and itchy nose, sneezing and nasal obstruction scores, and in the objective symptoms of nasal congestion and secretion after levocetirizine.

**Conclusions**

We could demonstrate, that the level of efficacy and the onset and duration of action of the 2 studied antihistamines were maintained to the same extent regardless of whether the subjects were suffering from SAR or PAR.

The results presented here demonstrate that levocetirizine and loratadine are well tolerated in the treatment of both SAR and PAR and that both are effective in alleviating the symptoms of allergic rhinitis compared with placebo. Levocetirizine was superior to loratadine in improving the symptoms of SAR in subjects challenged with grass pollen in the VCC. In addition, a trend toward superiority of levocetirizine compared with loratadine was demonstrated in subjects with PAR challenged with HDM. The development of methodologies such as the VCC allows a more natural, and yet a more controlled, comparison of treatments and may distinguish important differences between antihistamines, which could aid the treating physician in choosing the most effective therapy from the wide array currently available for allergic rhinitis.
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References


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