Efficacy and Tolerability of Astemizole-D and Loratadine-D During Prolonged, Controlled Allergen Challenge in the Vienna Challenge Chamber

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Summary

This randomized, double-blind, single-dummy, cross-over trial was initiated to compare the efficacy and tolerability of once-daily astemizole-D (CAS 141623-30-5; 10 mg astemizole/240 mg pseudoephedrine) with twice-daily loratadine-D (CAS 132316-36-0; 5 mg loratadine/120 mg pseudoephedrine) during prolonged, controlled allergen challenge in the Vienna Challenge Chamber. Twelve atopic patients participated in this study with a treatment duration of 3 days. Pollen challenges were made on days 1 and 3: the first to assess onset of drug action; the second to determine duration of drug effect. Drug efficacy was assessed using a number of standard objective and subjective measures. Onset of action was found to be generally comparable in both treatment groups for all parameters tested with a mean overall onset of action of 65 min during treatment with astemizole-D compared with 70 min on loratadine-D. As expected, astemizole-D tended to have a longer duration of action, with symptom severity lower with this agent than with loratadine-D during the second challenge session despite the differences in dosing schedule. However, inter-group differences did not attain statistical significance. Patient evaluations of therapeutic efficacy confirm these findings. Both drugs were well-tolerated, although a non-significant trend towards greater sleep impairment was seen during treatment with loratadine-D. In conclusion, astemizole-D was shown to be at least as effective and well tolerated as loratadine-D for the treatment of allergen-induced rhinoconjunctivitis during prolonged, controlled allergen challenge.

Zusammenfassung

Wirkung und Verträglichkeit von Astemizol-D und Loratadin-D während einer kontrollierten Langzeitbelastung in der Wiener Provokationskammer

Ziel der Studie ist es, die Wirkung und Verträglichkeit von einmal täglich verabreichtem Astemizol-D (CAS 141623-30-5; 10 mg Astemizol/240 mg Pseudoephedrin) und zweimal täglich eingenommenem Loratadin-D (CAS 132316-36-0; 5 mg Loratadin/120 mg Pseudoephedrin) während kontrollierter Allergenbelastung in der Wiener Provokationskammer, zu vergleichen. Das Studiendesign war randomisiert, doppelblind, single-dummy und cross-over. An der Studie nahmen 12 Graserpollenallergiker teil, die Behandlungsduer betrug 3 Tage. Am 1. und am 3. Tag wurde eine Langzeit-Pollenbelastung durchgeführt: die erste zur Festsetzung des Wirksamkeitsbeginns, die zweite, um die Wirkungsdauer der Medikamente zu eruiern. Um die Medikamentenwirkung zu dokumentieren, wurden eine Reihe von objektiven und subjektiven Meßmethoden angewendet. Der Wirksungsbeginn war mit einem durchschnittlichen Gesamtwirkungseintritt von 65 min nach Astemizol-D verglichen mit 70 min nach Loratadin-D-Behandlung für alle getesteten Parameter in beiden Behandlungsgruppen generell vergleichbar. Wie erwartet zeigte Astemizol-D nach 3 Behandlungstagen trotz der Einfachdosierung eine längere Wirkungsdauer mit geringerer Symptomatik als Loratadin-D. Dennoch gab es innerhalb der Gruppen keine statistisch signifikanten Unterschiede, was auch durch globale Patientenangaben über die therapeutische Wirkung bestätigt wurde. Beide Medikamente wurden gut vertragen, wenngleich während Loratadin-D-Medikation etwas mehr Schlafstörungen festgestellt werden konnten. Zusammenfassend kann gesagt werden, daß sowohl Astemizol-D als auch Loratadin-D eine vergleichbare Wirksamkeit und Verträglichkeit für die Behandlung der allergischen Rhinokonjunktivitis während kontrollierter Langzeitprovokation zeigen.

Key words Antihistaminic drugs · Astemizole-D · CAS 132316-36-0 · CAS 141623-30-5 · Histamine H1-receptor antagonists · Loratadine-D · Pseudoephedrine
1. Introduction
Non-sedating oral antihistamines, such as astemizole (CAS 141623-30-5) and loratadine (CAS 132316-36-0), are commonly used as first-line therapy in patients with allergic rhinoconjunctivitis [1]. However, clinical experience has shown that while these agents are effective for the treatment of ocular symptoms and nasal symptoms of sneezing, rhinorrhea and nasal itching, nasal congestion may persist necessitating concurrent administration of an oral or intranasal decongestant [2, 3]. Oral decongestants are better suited to the management of nasal congestion in this patient population as intranasal decongestants are only suitable for short-term therapy due to the potential for rebound and the development of tachyphylaxis during prolonged use [1]. As a result, a number of oral antihistamine/decongestant combination formulations have recently been developed with the aim of providing complete control of all symptoms in patients with allergic rhinoconjunctivitis [4–11].

These antihistamine/decongestant combination formulations are generally well-tolerated with the most common adverse effects associated with these agents, namely agitation and insomnia, attributable to the sympathomimetic effects of pseudoephedrine. Elevations in resting heart rate and systolic blood pressure have also been reported [12, 13]. Sleep studies have shown that 240 mg pseudoephedrine administered once-daily in the morning, either alone or in combination with an antihistamine, causes significantly less sleep impairment than is seen with more frequent dosing regimens [14, 15]. This is most likely due to the fact that evening plasma concentrations of pseudoephedrine are lower following administration of a single dose in the morning.

The present study was initiated to compare the efficacy and tolerability of a combination of 10 mg astemizole and 240 mg pseudoephedrine (astemizole-D) designed for once-daily administration with that of a commercially available combination of 5 mg loratadine and 120 mg pseudoephedrine (loratadine-D) administered twice-daily in patients with allergic rhinoconjunctivitis, with particular reference to onset and duration of action (peak and trough effects). In order to overcome one of the major limitations of environmental studies to assess the efficacy of antiallergic drug therapy, namely the wide inter-patient variation in pollen exposure due to differences in regional pollen counts and the amount of time spent outdoors, therapeutic efficacy was compared in the Vienna Challenge Chamber (VCC). This is an enclosed space designed to permit simultaneous, strictly controlled challenge of up to 12 subjects [16]. Previous studies using this approach have shown that a constant and reproducible distribution of allergen is achieved in the VCC [16, 17].

2. Materials and methods
2.1. Subjects
Twelve atopic volunteers, 9 males and 3 females aged between 22 and 30 years, took part in this trial. All of them were allergic to mixed grass pollen (defined by positive case history, positive skin prick test, grass pollen specific IgE (RAST Class 4) and positive nasal provocation test).

Exclusion criteria included: concurrent disease which might complicate investigation of the study drugs such as vasomotor rhinitis, rhinitis medicamentosa, active infective sinustis, upper respiratory tract infections or large obstructive nasal polyps; concomitant therapy which could interfere with the assessment of the drugs under investigation or result in treatment withdrawal period, for oral corticosteroids, 2 weeks for topical corticosteroids and sodium cromoglycate, 6 weeks for astemizole, and 3 days for other antihistamines, decongestants and any other drugs excluded by the study protocol; hyposensitization within 1 month prior to initiation of therapy; contraindications or precautions for pseudoephedrine use in patients with hypertension, hepatic or cardiovascular disease. Pregnant, nursing and fertile women without adequate contraception were also ineligible for participation.

2.2. Study design
This was a double-blind, single-dummy, cross-over trial. Subjects were randomized to receive either an astemizole-D capsule (10 mg astemizole plus 240 mg pseudoephedrine) with a loratadine-D placebo in the morning and matching placebos in the evening or a loratadine-D tablet (3 mg loratadine plus 120 mg pseudoephedrine) encapsulated in a wafer with an astemizole-D placebo twice daily with a treatment duration of 3 days. At least 4 weeks were allowed to elapse before cross-over.

The subjects were challenged in the VCC twice during each treatment period with dactylic grass pollen at a continuous concentration of 1000 grains/m³. The first allergen challenge commenced 1 h prior to administration of the first dose of trial medication to permit assessment of the onset of action. The second allergen challenge was conducted at the end of the treatment period, 10 h after administration of the final dose of study medication, to enable evaluation of the duration of action. Each allergen challenge lasted for a total of 3 h. The study design was approved by the ethics committee of the University of Vienna. All patients gave their written informed consent.

2.3. Assessments
Subjective assessments: During each allergen challenge, subjects evaluated the severity of individual nasal, ocular and pulmonary symptoms (nasal congestion, sneezing, nasal itching, rhinorrhea, ocular itching, lacrimation and wheezing) at 15-min intervals using a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). In addition, at the end of each challenge session, subjects provided an overall assessment of symptom severity using a Visual Analogue Scale (VAS) exceeding 100 = severe and assessment of global therapeutic efficacy rating the effect of therapy as excellent, good, moderate or poor.

Sleep quality and daytime alertness were assessed on both challenge days in terms of I) difficulty in falling asleep; II) night-time awakening; III) restlessness during sleep; IV) fatigue on waking in the morning; and V) fatigue during the day using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Subjects also provided VAS assessments of overall sleep quality and daytime alertness.

Objective assessment of nasal symptom severity was performed by I) weighing paper handkerchiefs collected at 30-min intervals to measure nasal secretions; II) measuring nasal airway resistance (NAR) and nasal flow at 75, 150 and 300 Pascal at 15-min intervals; III) measuring nasal peak inspiratory flow (PIF) at 15-min intervals.

Lung function was assessed by measuring forced inspiratory volume in 1 s (FI V₁) and maximal inspiratory flow (MIF) at 30-min intervals.

Resting blood pressure and heart rate were measured before each challenge session, and patients were requested to report any adverse experiences to the investigator at the end of each challenge session.

2.4. Calculations and statistics
An intention-to-treat analysis was performed. In addition to the individual symptoms listed above, the total symptom scores for all nasal symptoms, all ocular symptoms and all symptoms of rhinoconjunctivitis were calculated and analyzed. Onset of action was defined as the time to achieve I) a one-point decrease in the total symptom score [17, 18]; II) a decrease of 25% for nasal secretions, or III) a return to within 25% of baseline rhinomanometry parameters (nasal resistance, nasal flow and nasal peak expiratory flow). All inter-group differences were evaluated using the Mann-Whitney U-test. Treatment effects on the area under the curve (AUC) were assessed by means of one-way repeated analysis of variance testing (Koch analysis). Appropriate analyses for a cross-over design were performed.
Table 1: Baseline demographics in the two treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Astemizole-D / loratadine-D</th>
<th>Loratadine-D / astemizole-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (M/F)</td>
<td>7 (5/2)</td>
<td>5 (4/1)</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>24.9 (22–30)</td>
<td>26.0 (22–30)</td>
</tr>
<tr>
<td>Mean weight in kg (range)</td>
<td>71.4 (60–87)</td>
<td>74.8 (62–87)</td>
</tr>
<tr>
<td>Mean height in cm (range)</td>
<td>181.7 (168–196)</td>
<td>179.8 (170–190)</td>
</tr>
</tbody>
</table>

Table 2: Onset of action in the two treatment groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time of onset of action (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Astemizole-D</td>
</tr>
<tr>
<td>Rhinomanometry parameters</td>
<td>61.7</td>
</tr>
<tr>
<td>Nasal secretions</td>
<td>72.5</td>
</tr>
<tr>
<td>Subjective symptoms</td>
<td>65</td>
</tr>
<tr>
<td>Overall onset</td>
<td>65</td>
</tr>
</tbody>
</table>

Onset of action was defined as the time to achieve I) a return to within 25% of baseline rhinomanometry parameters; II) a decrease of 25% for nasal secretions; or III) a one-point decrease in total symptom score.

3. Results

As indicated in Table 1, the two groups were well-matched for the major demographic parameters. All subjects completed both challenge sessions. Appropriate analyses did not reveal any significant residual effects at cross-over, and consequently the data from the corresponding cross-over periods have been combined.

3.1. Onset of action

During the first allergen challenge session, the overall onset of action was found to be comparable in both treatment groups. In general, the effects of treatment on subjective symptoms and rhinomanometry parameters were seen within approximately 30 min of drug intake, with no consistent inter-group differences in therapeutic efficacy apparent. Mean overall onset of action was calculated to be 65 min during treatment with astemizole-D compared with 70 min on loratadine-D (Table 2) according to the calculation mentioned in paragraph 2.4. Total symptom severity scores were comparable in the two treatment groups throughout this challenge session (Fig. 1a). Treatment effects were apparent within 30 to

Fig 1: Subject assessment of total symptom severity in the two treatment groups. (a) first challenge session (peak); (b) second challenge session (trough).

Fig 2: Subject assessment of nasal symptom severity in the two treatment groups. (a) first challenge session (peak); (b) second challenge session (trough).
45 min of drug intake with a mean onset of action of 65.0 min for astemizole-D and 37.5 min for loratadine-D (p = 0.13). The severity of nasal symptoms and nasal secretions were also found to be similar in the two treatment groups (Fig. 2a and Fig. 3a, respectively), with Koch analysis failing to reveal any significant inter-group differences for these parameters. Ocular symptom severity was extremely low in both treatment groups throughout the allergen challenge with a peak score of less than 1 (mild) in both treatment groups. However, analysis of the AUCs for this parameter revealed a statistically significant difference in favour of loratadine-D (p = 0.018).

As shown in Table 2, onset of action as defined by the time to achieve a 25% decrease in nasal secretions was found to be similar in the two groups with a value of 72.5 min for astemizole-D and 77.5 min for loratadine-D. Koch analysis did not reveal any statistically significant inter-group differences for any of the rhinomanometry parameters evaluated, although an overall non-significant trend in favour of astemizole-D was apparent with a mean onset of action of 61.7 min compared with 77.5 min on loratadine-D (p = 0.09).

Subject assessments of global therapeutic efficacy confirm these findings (Fig. 4). At the end of this challenge session, 92% of subjects considered the effects of treatment with astemizole-D to be excellent or good compared with 75% on loratadine-D. However, inter-group differences did not attain statistical significance (p = 0.53). Patient VAS ratings of the overall severity of rhinoconjunctivitis were also comparable for the two study drugs.

3.2. Duration of effect

During the second allergen challenge, symptom severity was generally less severe during treatment with astemizole-D than with loratadine-D (Figs. 1b and 2b). Koch analysis revealed a trend favouring astemizole-D for the severity of nasal secretions (Fig. 3b; p = 0.07), but failed to reveal any statistically significant inter-group differences for any of the rhinomanometry parameters evaluated.
Patient evaluations confirm these findings (Fig. 4). At the end of this challenge session, 67% of patients rated global therapeutic efficacy to be excellent or good during treatment with astemizole-D compared with 75% for loratadine-D (p = 0.94). Patient VAS ratings were also comparable for both treatment regimens (p = 0.53).

3.3. Tolerability

Both astemizole-D and loratadine-D were well-tolerated. No significant inter-group differences in sleep quality and daytime alertness were reported, although some increase in night-time waking and restlessness during sleep was observed during treatment with loratadine-D, but not with astemizole-D.

Three subjects reported adverse events during the course of the trial (one case of dyspepsia in the astemizole-D treatment group with one report of tiredness and another of leg cramps while on loratadine-D). Slight increases in resting pulse rate and systolic blood pressure were observed in both treatment groups. There were, however, no significant differences between treatments.

4. Discussion

The results of this study demonstrate that once-daily treatment with astemizole-D is as effective as twice-daily loratadine-D for the treatment of allergen-induced allergic rhinoconjunctivitis during prolonged, controlled allergen challenge. Inter-group differences generally failed to attain statistical significance, however this is not surprising in view of the small patient population.

No consistent inter-group differences in onset of action were apparent. Overall onset of action was similar in the two treatment groups. Loratadine-D appeared to provide more rapid relief from ocular symptoms than astemizole-D, while onset of action as defined by the severity of rhinomanometry parameters tended to be more rapid with astemizole-D than with loratadine-D. Previous studies have also shown that the onset of action is as rapid with astemizole as with other non-sedating oral antihistamines [17, 19].

As expected, a trend towards prolonged duration of action for astemizole-D compared with loratadine-D was apparent. Symptom severity was lower with astemizole-D during the second challenge session than with loratadine-D, despite the differences in dosing schedule, with no significant inter-group differences in patients' global evaluations of therapeutic efficacy at the end of the challenge. This confirms the observations made in a previous VCC study, and demonstrates the long duration of action of astemizole and the effectiveness of once-daily dosing [17].

Both astemizole-D and loratadine-D were well-tolerated during this trial. As expected from the results of previous sleep studies [14, 15], more patients reported sleep impairment during treatment with loratadine-D than with astemizole-D although inter-group differences did not attain statistical significance.

However, statistically significant differences in favour of astemizole-D have been reported previously (Janssens et al., submitted for publication). This effect is most probably due to the fact that evening plasma concentrations of pseudoephedrine are lower following administration of astemizole-D in the morning than with twice-daily administration of loratadine-D.

In conclusion, astemizole-D appears to be at least as effective and well tolerated as loratadine-D and should therefore be considered a primary option for the treatment of allergic rhinoconjunctivitis.

5. References


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