Onset and Duration of the Effects of Three Antihistamines in Current Use – Astemizole, Loratadine and Terfenadine Forte – Studied During Prolonged, Controlled Allergen Challenges in Volunteers

FHORAK, SJÄGER AND UBERGER

First Ear, Nose and Throat Clinic, University of Vienna, Vienna, Austria

In a three-way, double-blind, crossover study the onset of action and effects at the end of the dosing interval of 10 mg/day astemizole, 10 mg/day loratadine and 120 mg/day terfenadine forte given for 3 days to six atopic volunteers were assessed using the Vienna challenge chamber (VCC). With each treatment, two long-term pollen challenges were performed in the VCC: the first to assess the onset of action started 1 h before the first dose and lasted continuously for 5 h; the second to assess the effects at the end of dosing took place 21 h after the last of the three doses and lasted 3 h. All three drug treatments initiated 1 h after the beginning of challenge with grass pollen reversed the adverse effects of challenge on the subjective symptoms (runny, blocked or itchy nose, sneezing, itchy eyes, tears) and the objective parameters (nasal secretions, nasal resistance, nasal flow, flow increase, nasal peak flow) within 1 – 3 h. The mean time to onset of action was 107 min for astemizole, 117 min after treatment for loratadine and 153 min for terfenadine forte.
During the second allergen challenge, 21–24 h after intake, astemizole consistently provided better protection for all parameters than did loratadine or terfenadine forte; however the differences were not statistically significant.

In einer doppelblinden Dreiwege-Crossover-Studie wurden der Wirkungsbeginn und die Effekte am Ende des Dosierungsintervalls von 10 mg/Tag Astemizol, 10 mg/Tag Loratadin und 120 mg/Tag Terfenadin forte beurteilt. Die drei Medikamente wurden für die Dauer von 3 Tagen an sechs allergische Freiwillige verabreicht. Für die Beurteilung wurde die “Wiener Provokations-Kammer” benutzt. Mit jeder Behandlung wurden zwei langzeitige Pollenexpositionen in der Wiener-Kammer durchgeführt. Die erste Exposition, die 1 h vor Verabreichung der ersten Dosis begonnen wurde, diente der Abklärung des Wirkungsbeginns und wurde ununterbrochen über 5 h fortgeführt, wohingegen die zweite zur Abklärung der Effekte am Ende der Dosierung, 21 h nach der letzten der drei Dosen vorgenommen wurde und 3 h dauerte. Mit allen drei medikamentösen Behandlungen, die 1 h nach Beginn der Provokation mit Graspollen eingeleitet wurden, konnten die klinisch erfaßbaren Wirkungen der Provokation auf die subjektiven Symptome (laufende, verstopfte oder juckende Nase, Nießreiz, juckende Augen, tränen Augen) aufgehoben werden. Die objektiven Parameter (Sekretproduktion der Nase, Nasenwiderstand, Nasendurchfluß, Durchflußzunahme, Nasen-Peakflow) zeigten nach 1–3 h eine Verbesserung. Die mittlere Zeit bis zum Wirkungsbeginn betrug für Astemizol 107 min, für Loratadin 117 min nach der Behandlung und für Terfenadin forte 153 min. Während der zweiten Allergenexposition, 21–24 h nach der Einnahme, stellte Astemizol für alle Parameter gleichbleibend einen besseren Schutz bereit als Loratadin oder Terfenadin forte. Die Unterschiede waren jedoch nicht statistisch signifikant.

KEY WORDS: ASTEMIZOLE; LORATADINE; TERFENADINE; ANTIHISTAMINES; HAY FEVER, SEASONAL NASAL ALLERGY; VIENNA CHALLENGE CHAMBER; ALLERGEN CHALLENGE
INTRODUCTION
When the new 'non-sedating' antihistamines became available, with the introduction of terfenadine and astemizole in the early eighties, the treatment of hay fever improved considerably.

During the last few years the timing of the onset of action of the new antihistamines has become controversial. In numerous studies onset has been defined in a variety of ways and differences in definition are probably responsible for the widely varying times to onset that have been reported even for the same substance. Onset can probably only be assessed adequately in comparative trials where the same definition applies to all the drugs investigated. In some comparative trials astemizole has been reported to have a slower onset of action than either terfenadine or loratadine. However, other authors have reported no difference in the onset of action.

The aim of the present study was to compare the timing of the onset of action and the duration of action of three currently available drugs: astemizole, loratadine and a once-daily formulation of terfenadine (terfenadine forte).

PATIENTS AND METHODS
PATIENTS
The six volunteers (five males, one female; age range 20 - 30 years, mean age 24.8 years) enrolled to the study reported having conjunctival complaints and rhinitis during the grass pollen season. The duration of anamnestic allergic complaints was 5 - 23 years (mean duration 12.5 years).

A skin prick test was performed in addition to negative and positive control. The extracts used, which were standardized, were produced by Abello, Spain. The six volunteers enrolled had highly positive reactions to grass pollen (Dactylis glomerata) in skin prick tests. Additional sensitizations did not influence the trial because all of the patients were free of symptoms before the start of the challenge and there was no chance that they could come into contact with other allergens during the trial.

The six volunteers included in the study had positive results for Phadebas (Pharmacia) radio-allergosorbent test, ranging from class 3 to class 4 (average 3.6).

A standardized nasal provocation test using native D. glomerata pollen for challenge and active anterior rhinomanometry for evaluating nasal reactions was carried out for all volunteers. Each volunteer showed a positive nasal reaction in terms of subjective itching, sneezing and rhinorrhea, and an objective reduction of nasal flow (< 40%) as measured by active anterior rhinomanometry.

ALLERGEN CHALLENGE
The Vienna challenge chamber (VCC) is an enclosed space inside which up to nine subjects can be challenged under controlled and reproducible conditions for several hours. The chamber is charged with air from indoors which is cleaned, cooled, dried and then loaded with a qualitatively and quantitatively determined amount of allergen(s).

For this trial D. glomerata grass pollen grains were used (the same batch as was used for diagnostic purposes) at a stable concentration of 1000 pollen grains/m³ air throughout the
duration of long-term challenge; this concentration is of the order that can easily be found in the country on a normal summer's day. Using the VCC each individual inhaled about the same antigen concentration as they would be likely to inhale, out of doors, during the summer. The distribution of the allergen is constant and reproducible because of the special technique of pollen dispersal. The Vienna challenge chamber, therefore, satisfies the recommendations for specific challenge rooms of the Subcommittee on Broncho-provocation for Occupational Asthma.  

**STUDY DESIGN**

The onset and duration of action of standard oral doses of astemizole, loratadine and terfenadine forte were compared under standardized allergen challenge conditions.

The double-blind, three-way, crossover study was carried out at the time of year when grass pollen was not naturally present in the air. Study medication was taken once daily for 3 days, the daily dosage being 10 mg astemizole, 10 mg loratadine or 120 mg terfenadine forte. In the periods between the administration of the different medications, no other treatment was allowed. The washout period between treatments was 3 weeks.

For each treatment, two long-term allergen challenges were performed in the VCC. The first allergen challenge was started 1 h before the first dose of the study medication and was continued for another 4 h after drug intake to assess the time of onset of action (peak effect) compared with placebo in accordance with the previous pilot study. The second allergen challenge, which was carried out at the end of the 3-day treatment period 21 h after the last dose and which lasted 3 h, was intended to assess the effects at the end of the dosing interval (trough effect). Table 1 shows the time course of one of the three treatments, each of which was identical.

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**TABLE 1**

*Time schedule of the allergen challenges accompanying treatments, with 10 mg/day astemizole, 10 mg/day loratadine, or 120 mg/day terfenadine forte given to the six atopic volunteers*

<table>
<thead>
<tr>
<th>Day</th>
<th>Time of day</th>
<th>Time after start of challenge (h)</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.00</td>
<td>0</td>
<td>Start of allergen challenge</td>
</tr>
<tr>
<td></td>
<td>11.00</td>
<td>1</td>
<td>First intake of drug (random coded)</td>
</tr>
<tr>
<td></td>
<td>15.00</td>
<td>5</td>
<td>End of challenge</td>
</tr>
<tr>
<td>2</td>
<td>11.00</td>
<td>–</td>
<td>Second intake of drug</td>
</tr>
<tr>
<td>3</td>
<td>11.00</td>
<td>–</td>
<td>Third intake of drug</td>
</tr>
<tr>
<td>4</td>
<td>08.00</td>
<td>0</td>
<td>Start of allergen challenge</td>
</tr>
<tr>
<td></td>
<td>11.00</td>
<td>3</td>
<td>End of allergen challenge</td>
</tr>
</tbody>
</table>
During each challenge session the parameters listed below were recorded at 20-min intervals in each patient. The subjective symptoms recorded were nasal symptoms (runny nose, blocked nose, itchy nose, sneezing) and ocular symptoms (itchy eyes, tears), and each symptom was rated on a four-point scale (0, absent; 1, mild; 2, moderate; or 3, severe). The objective parameters were nasal secretion, which was measured by weighing paper handkerchiefs collected at 20-min intervals, the nasal resistance and the nasal flow of each nostril, and the total at 150 Pa, and the nasal expiratory peak flow, all measured by rhinomanometry.

**STATISTICAL ANALYSIS**

Descriptive statistics were mainly used for evaluation of the data because only six volunteers participated in the study. The absolute data and changes from baseline during the two challenge sessions were compared for each of the three treatments.

Areas under the curves were calculated and treatment effects on these values were assessed by a one-way repeated measures analysis of variance. To adjust for baseline variability, for each of the parameters, the median of the three values during the first challenge hour (i.e. before treatment) was subtracted from each post-treatment value. The baseline-corrected values for loratadine and terfenadine forte were then subtracted from those for astemizole, resulting in a value indicating the difference between the drugs.

The time of onset of action was calculated, with reference to the value at the start of drug treatment (i.e. 1 h after the start of the challenge), as the time to a decrease of one point in the total symptom score (as proposed by Knight\(^{4}\)), a 25% decrease in nasal secretions, or a return to within 25% of the baseline values for the rhinomanometry parameters (nasal resistance, nasal flow and nasal peak expiratory flow). These arbitrary limits were suggested by statisticians, but have not previously been applied universally. The same criteria were, however, used for all three drugs in this comparative study. A mean time of onset of action was determined from the calculated onset times for the various parameters.

**RESULTS**

**ONSET OF ACTION**

During the first allergen challenge the effects of the challenge on subjective symptoms, nasal symptoms and objective nasal parameters were apparent within 20 min. Increases were observed in total symptom score, nasal secretions and nasal resistance, whereas decreases were detected in nasal flow parameters (nasal flow, nasal flow increase and nasal peak expiratory flow). Drug treatment, started 1 h after the beginning of the challenge generally reversed these effects 1 – 3 h later. Table 2 shows the effects at the end of the challenge (5 h) as percentage differences from the values at the start of drug treatment (1 h).

Total symptom score (Fig. 1a), which had increased dramatically during the 1-h treatment-free pollen challenge, decreased immediately or within 20 – 40 min after drug intake. At the end of the challenge the total symptom score was reduced by 64% after treatment with astemizole, 53% after loratadine and 49% after terfenadine forte.

Nasal secretion (Fig. 2a) increased rapidly during the 1-h pollen challenge before drug treatment, an average of 3.73 g mucus being produced during this period. After drug intake reduced nasal secretion was obvious in all three treatment groups. The increase produced at the end of the challenge was largest for astemizole (−82%) compared with −74% and −75% for loratadine and terfenadine forte, respectively.
Differences between symptoms and parameters measured at the end of the first allergen challenge (after, 5 h) and at the start of treatment (1 h after challenge initiation) for six atopic volunteers treated with 10 mg/day astemizole, 10 mg/day loratadine, or 120 mg/day terfenadine forte.

**TABLE 2**

Percentage change in parameter over the 4 h following treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Astemizole</th>
<th>Loratadine</th>
<th>Terfenadine forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score, maximum</td>
<td>-64%</td>
<td>-53%</td>
<td>-49%</td>
</tr>
<tr>
<td>Nasal secretion</td>
<td>-82%</td>
<td>-74%</td>
<td>-75%</td>
</tr>
<tr>
<td>Nasal resistance</td>
<td>-19%</td>
<td>-11%</td>
<td>+4%</td>
</tr>
<tr>
<td>Nasal flow</td>
<td>+20%</td>
<td>+4%</td>
<td>-7%</td>
</tr>
<tr>
<td>Flow increase</td>
<td>+39%</td>
<td>+24%</td>
<td>+9%</td>
</tr>
<tr>
<td>Nasal peak flow</td>
<td>+25%</td>
<td>+4%</td>
<td>+18%</td>
</tr>
</tbody>
</table>

**FIGURE 1**

Total symptom score during (a) the first allergen challenge and (b) the second allergen challenge in six atopic volunteers treated with 10 mg/day astemizole, 10 mg/day loratadine, or 120 mg/day terfenadine forte.
Nasal resistance (at 150 Pa) significantly increased during the first hour of challenge (average increase 59%). After an initial further increase after drug intake, nasal resistance started to decrease but at the end of the 5-h challenge session, nasal resistance was still above baseline in all three treatment groups, although the decrease was more with astemizole (−19%) than with loratadine (−11%) or terfenadine forte (+4%).

Nasal flow at 150 Pa was greatly reduced after 1 h of pollen challenge without treatment: from an average of 885 ml it declined to 614 ml (a reduction of 31%). At the end of the challenge, nasal flow increased by 20% compared with the start of drug treatment after treatment with astemizole, whereas only a small increase was detected with loratadine (4%) and with terfenadine forte there was a further reduction 7% in nasal flow.

Nasal expiratory peak flow after 1-h pollen challenge without treatment was reduced by an average of 24%. Return to baseline was nearly achieved following astemizole (95% of baseline) and terfenadine forte treatment (90% of baseline), but not after loratadine (79% of baseline).

The analysis of variance did not indicate any statistically significant differences between astemizole, terfenadine forte and loratadine with respect to onset of action for any of the parameters measured during the 4-h observation period.

The paired comparisons indicating the differences in treatment effects between astemizole and the other two drugs showed astemizole to be consistently better than loratadine and terfenadine forte for total symptom score (Fig. 3), this difference being almost significant (P < 0.1) for the comparison of astemizole and terfenadine carried out at 20 and 40 min after intake.
Paired comparisons of total symptom score during the first allergen challenge (peak) and the second allergen challenge (trough) between (a) astemizole and loratadine, and (b) astemizole and terfenadine forte; P < 0.1 astemizole compared with comparator antihistamine.

**TABLE 3**

*Time for onset of drug action on various parameters after treatment of six atopic volunteers with 10 mg/day astemizole, 10 mg/day loratadine, or 120 mg/day terfenadine forte*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Astemizole</th>
<th>Loratadine</th>
<th>Terfenadine forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>40</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Nasal secretion</td>
<td>40</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Nasal resistance</td>
<td>80</td>
<td>120</td>
<td>&gt;240&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nasal flow</td>
<td>220</td>
<td>&gt;240&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;240&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Flow increase</td>
<td>180</td>
<td>180</td>
<td>&gt;240&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nasal peak flow</td>
<td>80</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>Mean</td>
<td>107</td>
<td>117</td>
<td>153</td>
</tr>
</tbody>
</table>

<sup>a</sup> Indicates no 'onset' within the 4-h treatment period
Maximal effects of treatment following the second allergen challenge (trough) expressed as differences from baseline before challenge (0 h) in six atopic volunteers treated with 10 mg/day astemizole, 10 mg/day loratadine, or 120 mg/day terfenadine forte.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Astemizole</th>
<th>Loratadine</th>
<th>Terfenadine forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal resistance</td>
<td>+36%</td>
<td>+57%</td>
<td>+53%</td>
</tr>
<tr>
<td>Nasal flow</td>
<td>-24%</td>
<td>-34%</td>
<td>-37%</td>
</tr>
<tr>
<td>Flow increase</td>
<td>-23%</td>
<td>-38%</td>
<td>-37%</td>
</tr>
<tr>
<td>Nasal peak flow</td>
<td>-22%</td>
<td>-23%</td>
<td>-30%</td>
</tr>
</tbody>
</table>

(a) Sum of total symptom scores and (b) sum of nasal secretions for six atopic at second allergen challenge for six atopic volunteers treated with 10 mg/day astemizole, 10 mg/day loratadine, or 120 mg/day terfenadine forte.
Determination at the time of onset of action for the various signs and symptoms resulted in the figures given in Table 3. For all three drugs, onset of action was faster for symptoms and nasal secretions than for nasal flow parameters. The mean time to onset of action was 107 min for astemizole, 117 min for loratadine and 154 min for terfenadine forte. Subjective symptoms had already started to improve after 40 min for astemizole and loratadine, and after 60 min for terfenadine forte.

**DURATION OF EFFECT**

During the second allergen challenge, which was started 21 h after the last (third) dose of medication, increases in symptoms were seen despite the drug treatment.

Table 4 shows maximal effects for the nasal flow parameters observed during the 3-h challenge, expressed as differences from baseline. Figure 4 shows the symptom scores and nasal secretions (expressed as the sums of values for the six volunteers) for the 3-h challenge period.

Total symptom score (Figs 1b and 4a) was lowest after astemizole: total score for astemizole was 19.5 compared with 26.8 for loratadine and 24.1 for terfenadine forte. The most obvious difference between the three treatments was seen in the case of blocked nose. Nasal secretion (Figs 2b and 4b) amounted to a total of 4.48 g in the astemizole group, in contrast to 7.33 g and 7.11 g for loratadine and terfenadine forte, respectively. Nasal
resistance showed maximal increases of 36% with astemizole, 53% with terfenadine forte and 57% with loratadine. Nasal flow values (at 150 Pa) showed a clear, but not significant reduction after about 1 h of challenge.

Analysis of variance did not show statistically significant differences between the three treatments for any of the parameters measured. This is, to a large extent, due to the limited number of subjects (n = 6) and the variability of the data. The paired comparisons showed consistently better symptom control with astemizole than with loratadine or terfenadine forte, as shown in Figs 3 and 5 for total symptom score and nasal secretions, respectively.

**DISCUSSION**

Nasal obstruction after allergen challenge is more dependent on other mediators than on histamine. Togias et al. observed, however, a decrease in leucotrienes and prostaglandins in nasal lavage after treatment with cetirizine, terfenadine (administered systemically), or azatadine (administered topically), and a decrease in albumin and TAME esterase, indicating blood vessel permeability. In recent studies, Liu et al. and Naclerio et al. found that histamine-1 receptor antagonists can also act as mast cell stabilizers. The results of a pilot study comparing a single dose of 10 mg astemizole with placebo and using the method of long-term challenge and monitoring used in the present study were consistent with the latter finding since the antihistamine had a significant (P = 0.03) effect on nasal obstruction compared with placebo.

Some recent publications assessing onset of action have claimed a slower onset of action for astemizole than for terfenadine, cetirizine, or loratadine, whereas others have reported no differences between astemizole and terfenadine. cetirizine (unpublished data), or loratadine. Comparison of the reductions in symptom scores from patient diaries also showed the slopes are always parallel. Apart from astemizole, the other new antihistamines have not been compared with one another with respect to onset of action.

The present study clearly shows that, under well-controlled and constant pollen challenge conditions, there is no difference in onset of action between astemizole, loratadine and once-daily terfenadine forte when taken 1 h after the initial challenge, i.e. after the initial onset of complaints. For all three drugs, challenge-induced effects were reversed 1 – 3 h after drug intake.

In contrast, a comparison between placebo and astemizole showed that patients treated with placebo had steady increases in nasal obstruction, itching and all the typical symptoms during the hours following challenge with no tendency towards early stabilization. A statistically significant (P = 0.03) difference was demonstrated for nasal flow in favour of the active drug.

The results of the present study are consistent with those of Knight, who found a similar onset of symptom control for the same three drugs. In addition, significant inhibition of histamine skin tests has been described 1 h after a single intake of astemizole as well as in the case of other antihistamines. Animal data also have demonstrated that significant protection is provided by all three drugs within 30 min after oral intake.

A recent large-scale study in France of 765 patients with allergic rhinitis showed that there were definite circadian rhythms in allergic symptoms, with early morning peak times for sneezing, stuffy nose and runny nose. These results were consistent with those of an earlier study. This finding underlines the importance of 24-h guaranteed efficacy for a once-daily antihistamine to be taken in the morning.

The data obtained in the present study confirm the 24-h efficacy of the three drugs.
investigated. Although there were no statistically significant differences between the three drugs, there were consistent trends in favour of astemizole.

The limited number of patients used in the present study prevented the use of statistical analyses with sufficient power to reach clear conclusions about the duration of action of the drugs studied. The study, nevertheless, suggests that more research should be done on the 24-h action of once-daily antihistamines.

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**Address for correspondence**

**Dr F Horak**

First Ear, Nose and Throat University Clinic, Lazarettgasse 14, A-1090 Vienna, Austria