Controller Comparison of the Efficacy and Safety of Cetirizine 10 mg o.d. and Fexofenadine 120 mg o.d. in Reducing Symptoms of Seasonal Allergic Rhinitis

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Abstract
Background: The efficacy, onset and duration of action and safety of cetirizine 10 mg o.d., fexofenadine 120 mg o.d., and placebo were compared in this investigator-blinded, crossover study involving the use of the Vienna Challenge Chamber. Methods: 40 volunteers with seasonal allergic rhinitis were exposed to a controlled grass pollen concentration for 6 h on 2 consecutive days. Subjective symptoms and objective measurements were recorded during the allergen exposure periods. Results: Both active medications were significantly more effective than placebo and had a comparable onset of action in alleviating the symptoms of seasonal allergic rhinitis. The efficacy of both active drugs was comparable for the first 4 h after administration of the drugs on day 1 and day 2. However from 22 to 24 h after the first dose cetirizine was significantly superior to fexofenadine for the major symptom complex score and for sneezing. Concerning the total symptom complex score at day 2 fexofenadine could not reach superiority to placebo. No serious adverse events were reported. Conclusions: Cetirizine and fexofenadine were significantly better than placebo, also in reducing the symptom of nasal congestion.

However cetirizine appears to have a longer duration of action than fexofenadine.

Introduction

Cetirizine is a potent, second-generation antihistamine with a high specificity for the H1 receptor [1], a rapid onset of activity and a full 24-hour duration of effect [2]. The efficacy of the drug has been established in seasonal allergic rhinitis [3, 4], perennial allergic rhinitis [5–7], and chronic idiopathic urticaria [8]. Cetirizine is minimally metabolized [9], crosses the blood-brain barrier with difficulty [10], has a low incidence of adverse effects [11] and a low potential to cause cardiac arrhythmias [12–15]. In addition, cetirizine has been shown to inhibit eosinophil recruitment in the skin, nose, eyes and lungs [16–20].

Cetirizine has been available in Europe since 1987 and has been shown to have a very good safety profile [11]. Indeed discontinuation rates of therapy due to adverse events are comparable to those of placebo [11].

Fexofenadine is a new second-generation antihistamine. It is indicated for seasonal allergic rhinitis at a recommended dose of 60 mg twice daily [21] or 120 mg o.d. [22] and for chronic idiopathic urticaria at a recommended dose of 180 mg o.d. [23]. It has been shown to be efficacious and safe in clinical trials [21–25] and was,
therefore, considered to be of interest to compare these two compounds in a placebo-controlled clinical trial.

The evaluation of clinical responses to H1 antagonists is hampered in ‘field trial’ situations by factors relating to the variability in the general environmental allergen load, the individual patient’s exposure to allergen and the assessment of allergic response to medication.

The most obvious factor affecting the variability in the environmental allergen load is the seasonal nature of variation in pollen release, which restricts the timing of ‘field studies’. However even during this time other factors come into play, which affect the pollen levels not only from year to year, but from location to location and indeed from day to day at any single place.

Factors influencing the variability in the individual patient’s exposure to allergen are those parameters which influence exposure and response to allergens. Of particular importance here is the variability in an individual patient’s personal habits with regard to time spent indoors during the allergen season. Other factors, many of which have as yet not been fully elucidated, also come into play when determining the effect the allergen exposure has on the individual patient. It is, therefore, not surprising that patients who, in previous years, experienced symptoms and have a positive skin test may only experience a mild allergic reaction to an allergen exposure at any given time.

The final item, which impedes a clear evaluation of the efficacy of H1 antagonists, is the collection of factors that influence the assessment of ‘allergic’ symptoms. These are most often related to the occurrence of medical problems such as concomitant respiratory tract infections but in any event they only add to the difficulties related to the objective evaluation of subjects.

The sum total of all of these confounding factors necessitate large numbers of subjects to be included in field studies in order to be able to achieve an acceptable level of statistical validity.

In order to compensate for some of these confounding variables two researchers developed techniques that allow the reproduction of situations where the environment and the pollen exposure can be controlled for cohorts of allergic patients over sustained periods. The first and most sophisticated system is the Vienna Challenge Chamber, situated at the ENT Clinic of the University Hospital Vienna [26]. Under these controlled and controllable conditions, valid comparisons of allergic medications can be made [27-32].

Materials and Methods

Subjects
Of the 45 volunteers who were enrolled into the study, 40 fulfilled the inclusion criteria and the necessary response criteria to the pollen exposure. Of these 1 additional patient dropped out before completing the study due to ‘feeling uncomfortable’ on an assessment day. The study results were, therefore, based on the data obtained from 39 subjects. The subjects ranged in age from 20 to 36 years and were enrolled, out of the allergy season, from March to May 1998.

All had to have had documented seasonal allergic rhinitis as defined by a clinical history with a positive RAST (≥ class 2) and a positive skin prick test for grass pollen performed within the preceding 12 months. Symptoms requiring treatment had to have been present for at least 2 years prior to enrollment in the study, for which subjects had to have received appropriate pharmacological therapy.

Subjects were excluded if they were pregnant, not taking effective measures of birth control or were suffering from known drug and/or alcohol abuse, allergy/intolerance to the study drugs or other piperazines or any of the constituents of the study preparations, nasal anatomical deformities leading to obstruction (>50%) or any episode of sinusitis within 30 days of study commencement. They were also excluded if they had taken systemic corticosteroids and/or astemizole within 6 weeks, ketotifen, nasal and/or ocular chromoglycate and/or topical corticosteroids within 2 weeks, systemic theophylline and/or any other antihistamines within 1 week and all sympathimimetics within 24 h prior to enrollment. In addition, ongoing desensitization, known cardiac, renal or hepatic insufficiency, prior enrollment in the study or concomitant participation in any other study were causes for exclusion. Finally, any subject having relevant laboratory test results more than 10% outside the normal range was also excluded.

Ethics committee approval was obtained in Vienna prior to the start of the study, and written informed consent was obtained from all subjects prior to enrollment.

Design of the Study
This was a placebo-controlled, investigator-blinded, randomized, balanced three-period, three-treatment crossover study. Each period consisted of 2 consecutive days of treatment followed by at least 1 week of washout. During the 2 consecutive days in each period, subjects were exposed twice to a controlled grass pollen concentration for 6 h in the Vienna Challenge Chamber as described below. On each of these days, a single dose of medication (placebo, cetirizine 10 mg or fexofenadine 120 mg) was administered 2 h after entering the Vienna Challenge Chamber.

In order to maintain study blinding, the study medication was placed directly upon the tongue of each participant who kept his or her eyes closed during this procedure. They were instructed to swallow their study medication immediately, with the help of a glass of water that was provided.

Assessments
Inclusion and exclusion criteria, demographic data, clinical history of seasonal allergic rhinitis and current and previous medications for the disease were verified and recorded at enrollment.

During the time spent in the Vienna Challenge Chamber the following objective and subjective parameters of efficacy were assessed on a regular basis. Nasal congestion was measured by anterior rhinomanometry and nasal secretion was measured by weighing nasal handkerchiefs every 30 min. The subjective symptoms of sneezing

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runny nose, itchy nose, nasal obstruction, watery eyes, itchy eyes/ears, itchy throat and cough were recorded by patients on a 4-point scale, ranging from 0 (absent) to 3 (severe) every 15 min. Global evaluation of efficacy and satisfaction were each recorded by patients on a 100-mm Visual Analogue Scale every 15 min. Safety was monitored continually and a forced expiratory volume in 1 s was recorded every 30 min.

**Statistical Analysis**

Four distinct areas under the curve (AUC) were computed for each objective and subjective efficacy parameter: for both the two first hours (0–2 h) spent in the Vienna Challenge Chamber before drug intake as well as for the last 4 h (2–6 h) in the Vienna Challenge Chamber on both day 1 and 2 for each of the three study periods. The AUCs were computed according to the trapezoidal rule.

All statistical evaluations were performed separately on each of the AUCs. Parametric data were analyzed by means of ANOVA techniques and nonparametric data were analyzed using the Friedman test [33, 34]. If the test resulted in a global significant difference between the groups, then differences of rank sums between the groups (pairwise) were evaluated using multiple comparisons according to Wilcoxon and Wilcox [35]. Pairwise comparisons were performed only if the null hypothesis of equal efficacy between medications was rejected.

For the Friedman test exact p values can be presented. These p values were presented using three significant postcomma positions. If these three positions were zero, the last position was rounded to one. (For some tests the p value resulted in p = 0.00000 plus one nonzero digit.) The multiple comparisons according to Wilcoxon and Wilcox compare differences in rank sums and present critical rank sums for p values of 0.1, 0.05 and 0.01. Thus the only (but sufficient) information is whether the rank sum exceeds the critical value for (in our study) three groups and 39 subjects (resulting in p < 0.05, two-sided) or not (significant).

**End Points**

The primary outcome variables were the major symptom complex, defined as the sum of the symptom scores for runny nose, itchy nose, sneezing and watery eyes, and the total symptom complex, defined as the symptom scores for the major symptom complex with the addition of the symptoms of itchy eyes/ears, itchy throat and cough.

**Power of the Study**

Due to a lack of prior information concerning the expected magnitude (mean and standard deviation) of response to fexofenadine under the conditions prevailing in the Vienna Challenge Chamber, the calculation of the numbers of patients required in the study was based solely on our previous experience with cetirizine. The study was designed so as to be able to detect a difference between cetirizine and placebo at the 5% level of significance.

**Severity of the Rhinitis**

To remain eligible for the study, subjects were required to have a symptom severity score of at least 10 on day 1 for each study crossover period 2 h after entering the Vienna Challenge Chamber. The severity score was defined as the sum of the symptom scores of the major symptom complex, itchy eyes/ears and itchy throat.

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**Table 1. Demographic data of subjects (mean ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>Evaluated patients (n = 39)</th>
<th>Dropouts (n = 6)</th>
<th>Randomized patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>20 (51.3%)</td>
<td>5 (13.3%)</td>
<td>25 (55.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (48.7%)</td>
<td>1 (16.7%)</td>
<td>20 (44.4%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>25.6 ± 3.8</td>
<td>26.1 ± 5.3</td>
<td>25.7 ± 4.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.5 ± 12.7</td>
<td>73.3 ± 4.6</td>
<td>69.1 ± 12.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.6 ± 9.4</td>
<td>179.2 ± 7.3</td>
<td>176.1 ± 9.1</td>
</tr>
<tr>
<td>Skin prick test (positive)</td>
<td>5 (12.8%)</td>
<td>0</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Skin prick test (very positive)</td>
<td>34 (87.2%)</td>
<td>6 (100%)</td>
<td>40 (88.9%)</td>
</tr>
</tbody>
</table>

**Rescue Medication**

No treatment for rhinitis was permitted during the study. However, as it was anticipated that some subjects would experience asthmatic symptoms during the time spent in the Vienna Challenge Chamber the use of a local β2-mimetic inhaler was allowed on an as required basis.

**Changes to the Protocol**

Two amendments were made to the protocol. Firstly the total number of subjects to be included into the study was increased to 42 to ensure that there would be full data on at least 36 of these at the end of the study. In addition no subject, who had been withdrawn, was to be replaced during the study, and secondly, all subjects were required to have had a positive RAST and/or skin prick test within the 2 years prior to study enrollment.

**Vienna Challenge Chamber**

The Vienna Challenge Chamber can accommodate up to 14 subjects at any given time, all of whom were under constant supervision by staff outside. Communication is possible through windows and by an intercom system. The chamber was charged with indoor air, which was cleaned, cooled, dried, and then loaded with a qualitatively and quantitatively determined allergen load. Allergen concentrations, temperature and humidity were monitored every 5 min. A constant humidity of 30%, a temperature of 24° C and an allergen load, at a stable concentration of 1,500 pollen grains/m³, were maintained throughout the exposure period. The grass pollens were the same as used for diagnostic purposes and the distribution of the pollen was maintained by the dispersal system of the Vienna Challenge Chamber. These conditions simulate those found outdoors on a typical warm Austrian summer’s day.

**Results**

Thirty-nine subjects completed the study and were fully evaluated. Five subjects were prematurely withdrawn from the study due to an inadequate response to the pollen exposure. A further patient dropped out due to feeling
uncomfortable on a study day. No statistically significant differences emerged between any of the groups of subjects at baseline (tables 1, 2).

Statistically significant differences (p < 0.05) in favor of both cetirizine and fexofenadine emerged from the major symptom complex data with respect to placebo on day 1, 2–6 h (fig. 1), and day 2, 0–2 and 2–6 h (fig. 2).

Additionally, statistically significant differences in favor of cetirizine when compared to fexofenadine on day 2, 0–2 h, i.e. between 22 and 24 h after the first study drug intake were also observed, demonstrating that cetirizine provides a more complete 24 h coverage.

A similar pattern of response was observed for the total symptom complex data with nasal obstruction (significant superiority of cetirizine and fexofenadine to placebo on days 1 and 2, h 2–6).

Concerning the total symptom complex on day 2, 0–2 h a statistically significant difference only emerged from the data comparing cetirizine and placebo. No such difference was observed in the comparison of the data from the fexofenadine-treated group.

For nasal symptoms, as measured by the score for runny nose, itchy nose, nasal secretion and number of sneezing events, statistically significant differences in favor of cetirizine and fexofenadine compared to placebo emerged from the data when compared to placebo on day 1, 2–6 h and day 2, 0–2 and 2–6 h (p < 0.05, tables 2, 3).

Cetirizine and fexofenadine reached significant superiority to placebo also concerning the symptom nasal obstruction on days 1 and 2, 2–6 h (fig. 3).

Some protection, not always significant, was also provided by both drugs on the symptoms of sneezing (as measured on the assessment scale), watery eyes, itchy throat and cough (table 2). However, no significant differences were observed in nasal flow, measured by active anterior rhinomanometry (data not shown).
Fig. 1. Evolution of the mean scores of the major symptom complex (maximum score: 16 during the total challenge session; n = 39). Day 1. CTZ = Cetirizine; FXF = Fexofenadine; Pla = placebo.

Fig. 2. Evolution of the mean scores of the major symptom complex (maximum score: 16 during the total challenge session; n = 39). Day 2. CTZ = Cetirizine; FXF = Fexofenadine; Pla = placebo.

Fig. 3. Evolution of the mean scores of nasal obstruction (maximum score 4) during the total challenge session (n = 39). Day 2. CTZ = Cetirizine; FXF = Fexofenadine; Pla = placebo.

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Statistically significant differences in favor of cetirizine emerged from the data with respect to sneezing when compared to fexofenadine on day 2, 0–2 h (p < 0.05, table 2). Fexofenadine, furthermore, could not reach significant superiority to placebo on the global satisfaction evaluation on day 2, 0–2 h, whereas cetirizine did (p < 0.05, table 3). On the parameter of the global efficacy evaluation statistically significant differences in favor of both cetirizine and fexofenadine emerged from the data in comparison to placebo for day 1, 2–6 h and day 2, 2–6 h (p < 0.05, table 3).

Remarkably, with the exception of nasal airflow, placebo-treated subjects experienced a quicker and/or greater worsening of symptoms for most of the study parameters during the second day of exposure than was experienced on the first.

No significant order effect could be stated of the taking of both medications (in sequence analysis the p value for the major symptom complex was 0.576 and also for the different symptoms p values were >0.5).

During the three study periods a total of 8 adverse events were observed in 5 subjects (11.1%), none of which were considered to be serious. One subject complained of bronchospasm (or peak expiratory flow decrease) on three occasions during the study, once in the cetirizine treatment group, and twice in the fexofenadine treatment group. The likely cause of these events was considered to be the allergen challenge. In addition the following adverse events were reported as having occurred in the placebo-treated groups: epistaxis in 2 individuals, ‘flow decrease’ in 1, and pronounced seasonal allergic conjunctivitis in 1 (the latter also considered likely to have been caused by the allergen challenge). No statistically significant differences emerged from the analysis of the data of intensity of these effects between the two active medications. The evaluation of causality between these events and the study medications was assessed as being ‘not related’ in all except the two cases of epistaxis where the relationship was evaluated as being ‘unlikely’. In this latter case, the most likely explanation was the manipulation during the active anterior rhinomanometry.

Discussion

We have shown that cetirizine and fexofenadine are both effective and well tolerated in grass-pollen-sensitive volunteer subjects when exposed to these allergens in a controlled environment chamber. The present results also confirm the value of the Vienna Challenge Chamber in being able to deliver a controlled and controllable dose of appropriate pollen to sensitive subjects. Such environmental chambers allow for the control of many confounding factors found under field trial conditions. This gives a much greater scope for the assessment of antiallergic medication in terms of when such studies can be undertaken and in allowing the evaluation of these medications in smaller numbers of subjects. In this way limiting the exposure of the subjects needed in a study can show valid differences between medications [26, 36].

The present study provides a number of interesting observations. The first of these is that the finding that a clear effect of both cetirizine and fexofenadine was observed on nasal obstruction when assessed subjectively. This could not be expected, since antihistamines up to now were not shown to be effective in alleviating nasal congestion. For that reason we primarily did not include this symptom into the primary criteria. Nevertheless, the effect of the active treatment on the subjective symptom was not reflected in objective measurements of anterior rhinomanometry. If we accept that the latter is the more reliable measurement to make, then it should be borne in mind that the subjective relief provided by active medications on nasal symptoms might not reflect truly reduced nasal obstruction.

The second observation is that, in most cases, clinical symptoms were found to be worse at the beginning of the second day of allergen challenge than the first. This might suggest a ‘priming’ effect of allergen exposure in the case of seasonal allergic rhinitis. Nevertheless, higher symptom scores were observed in the 2 h preceding the second allergen challenge, suggesting that the symptoms following the first had not yet fully subsided.

Several characteristics of both cetirizine and fexofenadine might explain the observed differences between both medications. Studies have shown that cetirizine exhibited, even after a single dose, an inhibitory effect on the migration of eosinophils in skin, nose, eyes and lungs after allergen challenge [16–20]. This potential antiallergic effect has up to now been shown for fexofenadine at therapeutic serum concentrations and could be of use in alleviating the symptoms during the late phase of the allergic reaction which occurs 6 h after allergen exposure. In addition, cetirizine has demonstrated inhibitory effects on the late phase of the allergic reaction in vivo at therapeutic concentrations [19, 37].

In conclusion, we have demonstrated that both cetirizine and fexofenadine are safe, well tolerated and significantly better than placebo in subjects suffering from seasonal allergic rhinitis when exposed to grass pollen under
the strictly controlled conditions of allergen exposure found in the Vienna Challenge Chamber. However cetirizine appears to have a longer duration of action than fexofenadine.

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References

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