Clinical Study of the Therapeutic Efficacy and Safety of Emedastine Difumarate versus Cetirizine in the Treatment of Seasonal Allergic Rhinitis

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Summary

\textbf{Objective:} The therapeutic efficacy and tolerability of emedastine difumarate (CAS 87233-62-3) in male and female Caucasian patients with seasonal allergic rhinitis as compared to cetirizine (CAS 83881-51-0) was evaluated.

\textbf{Methods:} The study was designed as a double-blind, randomised, parallel groups comparison of two antihistamines administered by oral route (emedastine 4 mg o.d. versus cetirizine 10 mg o.d.) in a population of 120 patients suffering from grass pollen allergic rhinitis. The duration of the treatment period was 14 days. Primary efficacy variable was a total symptoms score (including among symptoms nasal congestion, sneezing, rhinorrhea, nasal/throat/palate itching, eye itching and lacrimation) evaluated after 14 days of treatment vs. baseline value. Safety was assessed on routine laboratory assays and recording vital signs and adverse events (AEs).

\textbf{Results:} The between-group difference in primary efficacy variable averaged over the 2-week treatment period was not statistically significant. Results clearly showed that no significant difference exists between the two treatments as far as total symptoms score evaluated after 14 days of treatment vs. baseline values are concerned. Therefore, the efficacy profiles of the study medications are overlapping. The pattern and incidence of AEs was similar in both treatment groups. The most frequent AEs with both compounds were related to the CNS, headache being the most reported one. In particular, this study seems to disclose a slighter tendency to drowsiness with emedastine than with cetirizine.

\textbf{Conclusions:} Both drugs under investigation in this trial appear to be effective for relieving the symptoms of seasonal allergic rhinitis in Caucasian adult patients. The results demonstrate that emedastine 4 mg o.d. is comparable in efficacy to cetirizine 10 mg once daily in the symptomatic management of seasonal allergic rhinitis. Moreover, based on the results of this study, emedastine can be considered a safe and well-tolerated drug and its safety profile seems to resemble that of cetirizine.

Key words

- CAS 83881-51-0
- CAS 87233-62-3
- Cetirizine
- Emedastine, clinical studies, efficacy in seasonal allergic rhinitis, safety
- Rhinitis, seasonal allergic

Zusammenfassung

Klinische Studien zur therapeutischen Wirksamkeit und Sicherheit von Emesadiston-Difumarat im Vergleich zu Cetrizin bei der Behandlung der saisonalen allergischen Rhinitis


Ergebnisse: Es zeigte sich kein statistisch signifikanter Unterschied bezüglich des Primärparameters; beide Behandlungsgruppen waren nach 14 Tagen Therapie in der Differenz des Gesamt-Symptomscores zum Ausgangswert gleichwertig. Das Wirksprofil beider Substanzen stimmte überein. Auch die Art und Häufigkeit von Nebenwirkungen war bei beiden Medikamenten vergleichbar.

Die häufigsten unerwünschten Ereignisse betrugen bei beiden Substanzen das Zentralnervensystem, wobei Kopfschmerzen am häufigsten waren. Die Ergebnisse zeigten bei Emesadiston eine leichte Tendenz zur Schläfrigkeit als bei Cetrizin.

1. Introduction

Histamine H₁-receptor antagonists have an established role in the treatment of seasonal allergic rhinitis [1]. Compared with older compounds of this class of drugs, the newer, second-generation H₁-receptor antagonists have a more favorable safety profile, most notably a lack of sedation. They also appear to have anti-allergy effects in addition to histamine blockade, such as inhibition of release of inflammatory mediators, antagonism of these mediators and inhibition of eosinophil recruitment [2].

Emesadiston difumarate (1-(2-ethylthioethyl)-2-(4-methyl-1-homopiperazinyl)-benzimidazole difumarate, CAS 87233-62-3) is a novel H₁-receptor antagonist with anti-allergic activity and with a high therapeutic index [3-6], as shown by several studies of general pharmacology and by a first efficacy study conducted in 130 Caucasian out-patients affected by seasonal allergic rhinitis [7].

The present comparative study has been designed with the aim of assessing both the activity and tolerability of emesadiston 4 mg. For the efficacy assessment the following parameters were evaluated: nasal congestion, sneezing, rhinorrhea, nasal/throat/palate itching, eye itching and lacrimation. The hypothesis was that emesadiston may be equally as active as cetirizine. This was based on the results obtained in a pharmacokinetic-pharmacological trial investigating the quantitative time course of the skin response to histamine (induction of wheals and flares) in male healthy volunteers administered orally emesadiston 2 mg b.i.d. and 4 mg o.d., cetirizine 10 mg o.d. and placebo [8], where emesadiston was shown to be equivalent to cetirizine, even though in this experimental model the latter compound is the most potent one among H₁-receptor antagonists.

A further aim of the study was the evaluation of possible adverse events such as headache, sleepiness, mental dullness, restlessness and dizziness, by taking into account the frequency, severity and duration. The aim was also to compare the previous data obtained with 2 mg b.i.d. vs. 4 mg o.d. [9].

The trial was carried out in a single centre during the grass pollen season (daily mean grass pollen count per m³ higher than 20, mid May-mid June 1998) in Vienna (Austria).

2. Patients and methods

2.1. Study design

The study design was a single centre, double-blind, randomised, parallel-group study, comparing two antihistamines administered by oral route for 14 days (emesadiston 4 mg o.d.)
versus cetirizine 10 mg o.d.) in patients suffering from grass pollen allergic rhinitis.

The parallel group design was selected since it offered the advantage of increasing the probability that both treatment groups were treated during the same period and therefore had homogeneous exposures to pollen levels.

A single centre study (Allergie Zentrum Wien West) was selected in order to overcome different pollen expositions in different centres.

The study was approved by the Ethics Committee of Vienna (Austria) and was performed in accordance with the Declaration of Helsinki, current revisions and the Good Clinical Practice (GCP) Guidelines of the European Commission.

2.2. Study population

A total of 120 patients were randomly assigned to treatment with either emedastine difumarate or cetirizine. One hundred patients (48 females, 52 males) completed the trial as per protocol: 54 of them were treated with emedastine (54%) and 46 with cetirizine (46%). Prior to inclusion, all patients were informed about the procedures of the study and the risks involved and gave their written informed consent to participate in the study.

Each patient underwent a screening, including medical history and concomitant treatments, a physical examination and laboratory investigation.

Inclusion criteria were: Caucasian; 19–64 years old; positive history for seasonal allergic rhinitis of at least 2 years duration and for which pharmacological therapy was required; documentation of hypersensitivity to a grass by means of RAST within the last year; at least one nasal symptom with score ≥ 2, lasting two days.

Subjects fulfilling the following conditions had to be excluded from the study: clinically important abnormal physical findings which could interfere with the objectives of the study; de-sensitisation therapy during the previous year; concomitant therapy with other anti-histamines, corticosteroids, antibiotics, beta-agonists, anticholinergics or other drugs that may influence the rhinitis symptoms, hypnotics, sedatives or any other drug that may induce CNS depression; corticosteroids or asemitizole therapy by oral route in the previous 4 weeks; anticholinergic agents, sedatives, hypnotics, systemic antibiotics, sodium cromoglycate in the previous 7 days, topical corticosteroids, other antihistamines, decongestants in the previous 24 hours; infective rhinitis; nasal polyposis or other nasal/brochial abnormalities that may influence the rhinitis symptoms; positive pregnancy test; participation in the evaluation of any drug during the month before the start of the study; profession involving the usage of dangerous machinery; blood donation during the 3 months prior to this study; history of drug, alcohol or tobacco abuse (> 40–60 g/day alcohol; > 10 cigarettes/day).

Subjects attended the Clinical Institute at baseline, at the end of the 1st week treatment period (day 7), at the end of the 2nd week treatment period (day 14) and within 4 weeks from the completion of the trial (follow-up).

2.3. Study drug

Test formulation was emedastine difumarate slow release capsules, each containing 4 mg (Batch no. 02S; Kanebo Pharmaceuticals Ltd, Osaka, Japan, represented for this product in the European Union by Saluc Pharma SA, Geneva, Switzerland). Reference formulation was cetirizine 10 mg tablets. The experimental drugs were placed into identical gelatinous capsules to ensure blindness.

One capsule was taken daily before breakfast for 14 consecutive days, according to randomisation.

2.4. Assessment of efficacy

The main parameter for the evaluation of efficacy was the severity of the following symptoms/signs, assessed by the patient on his/her diary, at baseline and every day, in the morning and in the evening: nasal congestion, sneezing, rhinorrhea, nasal/throat/palate itching, eye itching and lacrimation, using a 4-point scale (where 0 = absent, no symptoms evident, 1 = slight, symptoms present, but not bothersome, 2 = moderate, symptoms present and bothersome, but not intolerable, 3 = severe, intolerable symptoms).

The severity scores of each symptom/sign in the morning and evening were added up in order to calculate the Total Symptom Score: the change from baseline in the 14th day Total Symptom Score was the primary efficacy variable.

The change from baseline in the 7th-day Total Symptom Score and in the 7th and 14th total morning score (sum of the five morning symptoms) and total evening score (sum of the five evening symptoms) were secondary efficacy variables.

The individual mean symptoms score was also evaluated as secondary efficacy variable.

Patients also assessed overall discomfort (overall nasal discomfort and overall eye discomfort) using a 10-cm (0 mm = no trouble; 100 mm = maximum trouble) visual analogue scale (VAS) at baseline and at each weekly visit, in presence of the Investigator. Discomfort was considered secondary efficacy variable.

In addition, both the patient and the Investigator were asked to express their opinion regarding the therapeutic efficacy, using a 4-point scale (where 0 = no effect on allergic rhinitis symptoms or impairment of symptoms, 1 = some allergic symptom improves, but overall discomfort is unchanged, 2 = allergic rhinitis symptoms and overall discomfort improved, 3 = allergic rhinitis symptoms and overall discomfort greatly improved). Patient and Investigator global assessments were considered secondary efficacy variables.

2.5. Assessment of safety

The safety of the two active treatments was evaluated on the basis of physical examinations (vital signs) and routine laboratory tests (haematology, biochemistry, urinalysis) performed at each visit. In addition, safety was assessed by monitoring adverse events during the study period and up to 30 days of follow-up.

2.6. Statistical methods

The collected data were analysed to describe the individual and clinical characteristics of the sample, to verify the adequacy of the randomisation and to test normality of distribution and homogeneity of variance.

The primary efficacy analysis was carried out according to explanatory (per protocol, PP) approach. The primary variable, transformed or non transformed, was analysed using one-way ANOVA.

The PP analysis of secondary efficacy variables was performed using the above mentioned ANOVA model (analysis of change from baseline), ANOVA for repeated measures, using baseline value as covariate (analysis of VAS) and chi square test (analysis of global assessment).
The safety analysis was carried out on all randomised patients, assessing nature, severity and frequency of AEs, including laboratory values outside the normal range, suggesting a clinically relevant abnormality. Test of significance was two-tailed and critic a value was fixed at 5%.

3. Results

One hundred and twenty Caucasian patients suffering from seasonal allergic rhinitis were recruited and 100 completed the study as per protocol. Fifty-four out of them (21 females, 33 males) were treated with emedastine (54%) and 46 (27 females, 19 males) with cetirizine (46%).

Eleven patients did not show nasal symptoms at baseline and therefore could not be included in the per protocol statistical analysis. One patient was a drop-out because of an AE (influenza), and 8 patients were protocol violators.

Within the trial period (mid May - mid June 1998) on 14 of 16 days the daily mean grass pollen count per m² was higher than 20 in Vienna (Fig. 4, see p. 671).

Based on the results of the comparison of two weeks of treatment with emedastine difumarate versus treatment of the same duration with cetirizine, emedastine (4 mg o.d.) was shown to be as efficacious as cetirizine (10 mg o.d.) in the symptomatic management of seasonal allergic rhinitis in Caucasian patients.

This is confirmed by the statistical analysis performed on all the efficacy parameters and in particular by the analysis of the primary efficacy variable: the total symptoms score after 14 days of treatment vs. the same figure at baseline.

The between-group difference in primary efficacy variable over the 2-week treatment period was not statistically different.

Results clearly show that no significant difference exists between the two treatments and therefore the efficacy profiles of the study medications are similar. By considering the time effect, emedastine treatment resulted to decrease the total symptoms score of 18.2% after 14 days of treatment whereas the reduction obtained after cetirizine was 31% (Fig. 1). However, considering the p values obtained for the analysis of the primary efficacy variable, no statistically significant differences were found between the two treatments (p-value was 0.597 for the ANOVA treatment effect. Detailed p-values are presented below Fig. 1).

Results obtained after one week of treatment are comparable to those achieved at the end of the treatment period (14 days).

Separate analysis of morning and evening symptoms scores lead to the same results, i.e. non significant difference between the two treatment groups. As for the time effect, the only significant variations observed at day 7 and 14 vs. baseline consisted in a greater reduction in the evening symptoms score for both emedastine and cetirizine. This may be explained by considering that both drugs were administered in the morning and they display a higher activity within the first 12 h post-administration.

When the global score related to signs and symptoms is sub-divided into the individual signs/symptoms (Table 1), the comparison revealed that emedastine was not significantly different from cetirizine in reducing all symptoms but was significantly more efficacious in reducing rhinorrhea, even after only 7 days of treatment (p = 0.036 for comparison vs. baseline) and in particular the percentage of reduction was 29% for emedastine and 21% (n.s.) for cetirizine. The percent reduction of rhinorrhea after 14 days treatment with emedastine was 66% whereas the decrease obtained with cetirizine was 64% as shown in Fig 2.

These data are in agreement with the results obtained in a previous study on the treatment of seasonal allergic rhinitis where emedastine was compared to terfenadine [7].

For overall discomfort felt by patients, no significant differences were evident between the two treatment groups, neither for nasal and eye discomfort, thus

**Table 1: Mean Individual Symptom Score (± SD) assessed by a 4-point scale at baseline, at the end of the first week and at the end of the second week of treatment with emedastine (E) and cetirizine (C).**

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2.44</td>
<td>2.38</td>
<td>2.35</td>
</tr>
<tr>
<td></td>
<td>(1.32)</td>
<td>(1.45)</td>
<td>(1.49)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1.77</td>
<td>1.84</td>
<td>1.61</td>
</tr>
<tr>
<td></td>
<td>(1.12)</td>
<td>(1.05)</td>
<td>(1.29)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1.66</td>
<td>1.76</td>
<td>1.19**</td>
</tr>
<tr>
<td></td>
<td>(1.22)</td>
<td>(1.31)</td>
<td>(1.42)</td>
</tr>
<tr>
<td>Nasal/throat/</td>
<td>1.79</td>
<td>1.84</td>
<td>1.62</td>
</tr>
<tr>
<td>palate itching</td>
<td>(1.26)</td>
<td>(1.44)</td>
<td>(1.23)</td>
</tr>
<tr>
<td>Eye itching and</td>
<td>1.57</td>
<td>1.59</td>
<td>1.76</td>
</tr>
<tr>
<td>lacrimation</td>
<td>(1.20)</td>
<td>(1.43)</td>
<td>(1.37)</td>
</tr>
<tr>
<td>Total score</td>
<td>10.39</td>
<td>10.78</td>
<td>8.89</td>
</tr>
<tr>
<td></td>
<td>(4.33)</td>
<td>(5.89)</td>
<td>(5.14)</td>
</tr>
</tbody>
</table>

Statistically significant decreases in the mean individual symptoms score vs. baseline are shown in italics (C p < 0.05; ** p < 0.01).
Fig. 2: Decreasing effect on rhinorrhea at baseline, at the end of the first week and at the end of the second week of treatment with emedastine (blank columns) and cetirizine (hatched columns). Rhinorrhea comparison of day 14 vs. baseline p-value was < 0.001 for both emedastine and cetirizine group and day 7 vs. baseline p-value was 0.036 for emedastine group and 0.107 for cetirizine group. Between groups comparison resulted in p-value 0.898 at baseline, 0.592 at day 7 and 0.699 at day 14.

Demonstrating once more that the test and the reference drugs have similar efficacy profiles. Cetirizine resulted to significantly decrease both kinds of discomfort after only 7 days of treatment while emedastine significantly reduced overall eye discomfort only after a prolonged administration (14 days) as shown in Table 2.

The global judgement expressed both by patient and investigator was not significantly different for the two treatments, thus confirming that the drugs under investigation in this study are comparable as far as global assessment is concerned. It is worthy of note the fact that in more than 45% of cases the investigator judged emedastine to improve patients conditions after 7 and 14 days of treatment whereas the positive judgement on emedastine raises to about 55% after 7 days of treatment and to about 50% after 14 days of treatment when evaluated by the patients (Fig. 3).

Results of the present study showed how both emedastine and cetirizine were well tolerated.

No clinically relevant findings occurred in any of the two treatment groups.

The analysis performed to evaluate the laboratory values out of normal ranges did not highlight any difference at day 14 vs. baseline for all parameters investigated in both treatment groups.

No SAEs occurred during the study. The pattern and incidence of AEs was similar in both treatment groups as shown in Table 3. Twenty patients (37%) suffered a total of 24 (42%) AEs during treatment with emedastine whereas 28 patients (61%) suffered 33 (56%) AEs during treatment with cetirizine (no statistical difference between the two treatment groups).

The recorded AEs and laboratory abnormalities are related to known adverse reactions to second generation anti-histamines [10].

The safety profile of the two drugs was very similar, also considering that no relation with emedastine treatment was assessed for 41.9% of AEs, whereas for cetirizine this figure was 19.2%.

Considering only adverse events possibly related to the study drugs, the most frequent AEs with both compounds concerned the central nervous system, headache being at the top of the list with 55.6% of patients treated with emedastine and 70.0% of patients treated with cetirizine. Drowsiness was reported by only 2 patients with emedastine (11.1%) and by 5 patients with cetirizine (25.0%) (see Table 3).

Table 2: Mean overall nasal and eye discomfort (± SD) at baseline and at each weekly visit.

<table>
<thead>
<tr>
<th>Overall nasal discomfort</th>
<th>Mean</th>
<th>SD</th>
<th>p value</th>
<th>Overall eye discomfort</th>
<th>Mean</th>
<th>SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emedastine</td>
<td>4.39</td>
<td>2.15</td>
<td>0.75</td>
<td>Cetirizine</td>
<td>4.61</td>
<td>2.34</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td>Day 7</td>
<td>3.56</td>
<td>2.56</td>
<td>0.005</td>
</tr>
<tr>
<td>Day 14</td>
<td>3.56</td>
<td>2.11</td>
<td>0.75</td>
<td>Day 14</td>
<td>3.56</td>
<td>2.02</td>
<td>0.002</td>
</tr>
</tbody>
</table>

The decrease of overall nasal discomfort was 19% for emedastine and 25% for cetirizine at day 7, while at day 14 decrease of nasal discomfort after emedastine administration remained at 19% and after cetirizine increased to 33%.

The decrease of overall eye discomfort after treatment with emedastine was 19% at day 7 and 24% at day 14. After treatment with cetirizine, decrease of eye symptoms was 20% at day 7 and 31% at day 14.
4. Discussion

Both the drugs under investigation appear to be effective for relieving the symptoms of seasonal allergic rhinitis. The results demonstrate that emedastine 4 mg o.d. is comparable in efficacy to cetirizine 10 mg once daily in the treatment of seasonal allergic rhinitis. The reduction of rhinorrhea at day 7 vs. baseline was significant (p = 0.036) only for emedastine group.

In addition, based on the safety data, emedastine can be considered a well-tolerated anti-histamine in the treatment of seasonal allergic rhinitis and its safety profile resembles that of cetirizine.

However, it the efficacy results of this trial may have been influenced by the following two factors:

- A higher ratio of females over males in the patient population of the cetirizine group vs. the emedastine group, corresponding to a higher cetirizine dose (expressed as mg/kg). This may lead to a higher response to the cetirizine treatment than to the emedastine one.

- For most patients included in this trial, the baseline evaluation of nasal symptoms was performed in a period of low pollen concentration, whereas the judgement of drugs efficacy, i.e. symptoms scores during the course of treatment and after 14 days of treatment, was made with a higher pollen concentration, as shown in Fig. 4. The increase of pollen concentration during the course of the trial resulted in a reduced patients’ response to the drugs action. Thus, the analysis of data (comparison of the TSS at baseline and after 14 days) and their statistical evaluation (time effect) underestimate the effectiveness of both drugs.

Table 3: Adverse events possibly related to the study drugs.

<table>
<thead>
<tr>
<th>Nature of event</th>
<th>Emedastine</th>
<th>Cetirizine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>No. of</td>
</tr>
<tr>
<td></td>
<td>events (%)</td>
<td>events (%)</td>
</tr>
<tr>
<td>CNS total</td>
<td>10 55.56</td>
<td>14 70.00</td>
</tr>
<tr>
<td>Headache</td>
<td>6 33.33</td>
<td>8 40.00</td>
</tr>
<tr>
<td>Strong headache</td>
<td>1 5.56</td>
<td>0 0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2 11.11</td>
<td>5 25.00</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 5.56</td>
<td>0 0</td>
</tr>
<tr>
<td>Concentration problems</td>
<td>0 0</td>
<td>1 5.00</td>
</tr>
<tr>
<td>Gastrointestinal total</td>
<td>0 0</td>
<td>2 10.00</td>
</tr>
<tr>
<td>Problems with stool</td>
<td>0 0</td>
<td>1 5.00</td>
</tr>
<tr>
<td>Permanent mouth dryness</td>
<td>0 0</td>
<td>1 5.00</td>
</tr>
<tr>
<td>Musculoskeletal total</td>
<td>6 33.33</td>
<td>2 10.00</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1 5.56</td>
<td>0 0</td>
</tr>
<tr>
<td>Heavy tiredness</td>
<td>0 0</td>
<td>1 5.00</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 22.22</td>
<td>0 0</td>
</tr>
<tr>
<td>Extreme fatigue</td>
<td>1 5.56</td>
<td>0 0</td>
</tr>
<tr>
<td>Pain of the limbs</td>
<td>0 0</td>
<td>1 5.00</td>
</tr>
<tr>
<td>Miscellaneous total</td>
<td>2 11.11</td>
<td>2 10.00</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1 5.56</td>
<td>0 0</td>
</tr>
<tr>
<td>Severe itching of eyes</td>
<td>1 5.56</td>
<td>0 0</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0 0</td>
<td>1 5.00</td>
</tr>
<tr>
<td>Sweating</td>
<td>0 0</td>
<td>1 5.00</td>
</tr>
<tr>
<td>Total</td>
<td>18 100.00</td>
<td>20 100.00</td>
</tr>
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5. Literature


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