A DOUBLE BLIND PARALLEL MULTISITE STUDY OF THE SAFETY AND EFFICACY 
OF CETIRIZINE COMPARED TO DEXCHLORPH PRA MINE AND PLACEBO 
IN THE TREATMENT OF CHILDREN WITH SEASONAL ALLERGIC RHINITIS

- CLINICAL REPORT -

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Trade name: ZyrtecR  
Generic name: cetirizine  
Code number: UCB P071 (- cetirizine 2HCl)  
Chemical name: {2-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl}ethoxy|acetic acid, dihydrochloride.
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I. INTRODUCTION

Cetirizine is a potent and selective H₁ antagonist with some additional antiallergic pharmacological properties: inhibition of eosinophil infiltration and reduction of histamine concentration in sites of antigen-antibody conflict.

Clinical experience to date in an adult population demonstrated the efficacy of a once daily dose of 10 mg in both seasonal and perennial allergic rhinitis and a favourable adverse reaction profile, with occasional mild drowsiness as the most frequently reported event. The toxicologic profile of cetirizine has not revealed any effects which would argue against its use in a pediatric population.

The objective of this multicenter study was to evaluate the safety and efficacy of cetirizine and dexchlorpheniramine versus placebo in the treatment of children with seasonal allergic rhinitis.
II. SUBJECTS AND METHOD

1. Aims of study

The aim of this study was to establish the efficacy and safety of cetirizine and to compare this to dextchlorpheniramine and placebo.

2. Study design:

This study was a randomized, double blind multisite parallel study with placebo control. A total of 48 patients were to be included in the study. They would be assigned to one of three groups of 16 patients each on the basis of a randomisation code:

3. Tests preparations, administration and dosage:

   Group D: cetirizine 7.5 mg once a day in the evening +
   placebo: one tablet in the morning and
   one tablet at noon.
   Group E: placebo - one tablet t.i.d.
   Group F: dextchlorpheniramine - 2 mg t.i.d.

4. Patient selection

To be included, the patients had to respond to the following criteria:
male or female out patients, between 11 and 14 years of age, with a
documented history of pollen related allergic rhinitis, sulfuring from
an acute episode characterized by any two of the following symptoms:
   - sneezing,
   - nasal itching,
   - rhinorrhea,
   - hyperemia of the nasal mucosa,
   - itching of the eyes or allergic conjunctivitis.

Patients with perennial allergic rhinitis could be entered if they were
suffering from an acute exacerbation of seasonal allergic rhinitis.

The allergic history had to be verified and confirmed by either a RAST
test or by skin testing.
At the final visit, a global assessment of the patients' condition was made and compared with that at the first visit. It consisted of the following gradation:

- complete relief (100 %)
- marked improvement (75-100 %)
- slight improvement (50 %)
- no improvement

Photographs of nasal mucosa had to be taken under fibroscopy 3 to 4 times during the study.
Count and analysis of eosinophils had to be performed 3 times.
At the initial visit, the patients were given self assessment cards and asked to complete them daily, each evening, from day 1 to day 15, evaluating the intensity of rhinorrhea, itching nose, sneezing, stuffy nose, itching eyes. They used a smile chart too.
At each visit, the patients evaluated their own status using a visual analog scale.

The patient had to drop out of the study if any of the initial laboratory values were significantly abnormal. Patients who were treated for at least 3 days were to be evaluated for efficacy. If they dropped out before day 3, they were not evaluable.

No rescue drug and no decongestant were to be used during the course of the study.
Could not be included:

- patients with an underlying disease that would interfere with the evaluation of the therapeutic response,
- patients with a history of allergic reaction to piperazines,
- patients with a current history of abnormal renal, hematologic or liver function tests,
- patients with acute bacterial sinusitis,
- chronic asthmatic patients requiring medication to control symptoms,
- patients who could not stop the use of nasal glucocorticoids or cromolyn for one week prior to the study or oral antihistamines for an average of 48 hours prior to the study. For ketotifen and astemizole this delay had to be 15 days.
- patients who needed substances having antihistaminic or sedating properties, e.g. phenothiazines, anticholinergic agents, sedatives, hypnotics, antiepileptics,
- patients who had received an investigational drug within the previous month,
- children weighing more than 50 kg.
III. RESULTS

The statistical analysis has been performed by CANDOR sprl, rue de la Treille, 19 - B 4200 Liège, Belgium.  
(See statistical report in Appendix).

The basal homogeneity of the 3 groups was studied by the way of an ANOVA (analysis of variance) for quantitative data and by the way of CHI squared for qualitative data.

To study the efficacy, an analysis of variance for repeated measurements was used with the HULNH-FELDT correction of the degrees of freedom to prevent some lack of homoscedasticity. The used values were the differences between the second and the first measures or between the third and the first measures.

48 patients were included in the study and distributed as follows:

- 16 received cetirizine
- 16 received placebo
- 16 received dexchlorpheniramine

Demographic characteristics

The mean age of the patients was:

(years) 12 ± 0.7 (11-14) in the cetirizine group  
12.2 ± 0.9 (11-14) in the placebo group  
11.8 ± 0.5 (11-13) in the dexchlorpheniramine group
The mean weight of the patients was:

(kg) \( 39.3 \pm 7.2 \) (26.5-50) in the cetirizine group

\( 39.6 \pm 6.8 \) (30 -50) in the placebo group

\( 39.3 \pm 6 \) (30 -50) in the dexchlorpheniramine group

They were suffering of seasonal allergic rhinitis since:

(years) \( 8.2 \pm 3.2 \) (2-12) in the cetirizine group

\( 5.9 \pm 3.3 \) (1-11) in the placebo group

\( 6.6 \pm 3 \) (2-11) in the dexchlorpheniramine group

There were 17 girls and 31 boys respectively

5 and 11 in group cetirizine

8 and 8 in group placebo

4 and 12 in group dexchlorpheniramine

Desensitisation was on going for:

2 patients in the cetirizine group

0 patient in the placebo group

4 patients in the dexchlorpheniramine group

Asthma was present in 1 patient in the cetirizine group.

Atopic dermatitis was present in no patient enrolled in the study.

Globally, the three groups of patients were not different at the beginning of the study.
Efficacy evaluation

The evaluation of the severity of the symptoms as registered at each visit is shown in table 1.

**TABLE 1**

Mean scores : 5 symptoms scored from 0 to 3 = 15 (maximum score)

<table>
<thead>
<tr>
<th></th>
<th>Cetirizine group</th>
<th>Placebo group</th>
<th>Dexchlorpheniramine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (−) *</td>
<td>14 (2)</td>
<td>12 (4)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Period of treatment (week)</td>
<td>0 1 2</td>
<td>0 1 2</td>
<td>0 1 2</td>
</tr>
<tr>
<td>Mean score</td>
<td>3 2.9 1.7</td>
<td>3.8 2.6 2</td>
<td>2.4 2.8 2</td>
</tr>
<tr>
<td>Difference % from week 0</td>
<td>- -3 -43</td>
<td>- -32 -47</td>
<td>- +17 -17</td>
</tr>
</tbody>
</table>

* (−) Number of patients with a score = 0 before treatment and therefore discarded from the analysis as being ineligible.

The more favourable evolution is seen in the placebo group; the worst results are registrated in the dexchlorpheniramine group.

As far as cetirizine is concerned, the reported results correspond to a mean dosage of 0.19 mg/kg ± 0.03 n = 14.
In separating the patients of this cetirizine group in 2 subgroups, one receiving less than 0.19 mg/kg, the other receiving 0.19 mg/kg or more, we find (Table 2):

**TABLE 2**

<table>
<thead>
<tr>
<th>Mean scores in cetirizine group</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>$\chi &lt; 0.19$ mg/kg $\leq \chi$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
</tr>
<tr>
<td>Period of treatment</td>
<td></td>
</tr>
<tr>
<td>Mean score</td>
<td>2.4</td>
</tr>
<tr>
<td>$\Delta%$</td>
<td>$-$</td>
</tr>
</tbody>
</table>

The improvement thus appeared more important in the group receiving a higher dose, which also happened to appear more symptomatic at the outset of the study.

The results of the analysis of self assessment rating scale (from 0 to 10) are shown in Table 3.
**TABLE 3**

Self assessment rating scale (from 0 to 10)

<table>
<thead>
<tr>
<th>Period of treatment</th>
<th>Cetirizine group</th>
<th>Placebo group</th>
<th>Dexchlorpheniramine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>4.5 ± 2.4</td>
<td>3.8 ± 3.4</td>
<td>5.1 ± 3</td>
</tr>
<tr>
<td>After one week</td>
<td>6.7 ± 2.2</td>
<td>6.6 ± 3.2</td>
<td>6.9 ± 2.6</td>
</tr>
<tr>
<td>After two weeks</td>
<td>6.9 ± 2.5</td>
<td>8.1 ± 2.8</td>
<td>7.2 ± 3.2</td>
</tr>
</tbody>
</table>

The global evaluation of the treatment made by the investigator and by the patient after one and two weeks of treatment is shown in Table 4.

**TABLE 4**

Global evaluation

<table>
<thead>
<tr>
<th></th>
<th>Cetirizine group</th>
<th>Placebo group</th>
<th>Dexchlorpheniramine group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By the investigator</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>1.9 ± 0.9</td>
<td>1.8 ± 0.4</td>
<td>2.1 ± 0.8</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.9 ± 0.8</td>
<td>1.6 ± 0.7</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td><strong>By the patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>2.25 ± 0.9</td>
<td>1.9 ± 0.6</td>
<td>2 ± 0.8</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.75 ± 0.9</td>
<td>1.8 ± 0.8</td>
<td>1.8 ± 1</td>
</tr>
</tbody>
</table>

(1 = poor; 2 = moderate; 3 = good; 4 = excellent).
Statistics

From the statistical point of view, no difference appeared between the three groups as well before as after treatment.

IV. DISCUSSION

In this study, placebo > cetirizine > dexchlorpheniramine but were however not significantly different, each improving the symptomatology of a patient population that was but mildly affected.

Several mutually non exclusive explanations for this outcome are possible:

1) The symptoms of too many patients may not have been due to pollinosis but rather to mild vasomotor rhinitis or upper respiratory tract virosis which cannot be expected to react to antihistamines, but would be expected to follow a course tending to spontaneous recovery, thus reinforcing a placebo effect.

2) The mildness of the initial symptomatology, and its tendency to improve under placebo may have masked any possible therapeutic effect of the antihistamines. The mildness of the symptoms may have been due to scantness of pollen. This cannot be verified since no pollen counts are available.

The study was carried out during the month of October 1986.

3) Compliance to trial medication intake may be cast in doubt in a so mildly affected population, that had to take three tablets a day and where no monitoring was performed.
4) Cetirizine treatment may have been inadequate because of:
   a) ineffectiveness on the pathology (considering its clear effectiveness in adults, this is rather unlikely).
   b) inadequate dosage: a mean dose of 0.19 mg/kg may be insufficient. This interpretation is supported by the fact that the patients with a higher dosage seemed to have a more pronounced effect.
   c) pharmacokinetics in children: later studies (UCB P3/2021) have demonstrated a more rapid elimination time in children than in adults, possibly necessitating b.i.d. doses.

   In view of the fact that diphenhydramine is standard effective treatment in the studied pathology, interpretations 1, 2 or 3 or a combination thereof seem the most likely. Since no side effects were noted, cetirizine usage was safe. However, its effectiveness cannot be evaluated from this study. To do this will require studies with a better defined and more marked pathology.

V. CONCLUSION

No conclusion can be drawn from that unsatisfying study.