A DOUBLE BLIND PARALLEL MULTISITE STUDY OF THE SAFETY AND EFFICACY
OF CETIRIZINE COMPARED TO DEXCHLOORPHENIRAMINE 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-(4-chlorophenyl)phenylmethyl -1-piperazinyl ethoxy)acetic acid,
dihydrochloride.

U C B, Pharmaceutical Sector
DRD, Clinical Research & Development
Chemin du Foriest
B-1420 Braine-l'Alleud
Belgium

YB/ZE/ea1
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I. INTRODUCTION

Cetirizine is a potent and selective $H_1$ antagonist with some additional antiallergic pharmacological properties: inhibition of eosinophil infiltration and reduction of and 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. Aim of study:
The aim of this study was to establish the efficacy and safety of cetirizine and to compare this to dexchlorpheniramine 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: dexchlorpheniramine - 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, suffering 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 seasonal exacerbation of allergic rhinitis.

The allergic history had to be verified and confirmed by either a RAST test or by skin testing.
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 study was carried out during August and September 1986.

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 a CHI squared for qualitative data.

To study the efficacy, an analysis of variance for repeated measurements was used with the HUYNH–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.

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

14 received cetirizine
14 received placebo
13 received dexchlorpheniramine
Globally, the 3 groups of patients were not different at the beginning of the study.
Efficacy

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><strong>n</strong></td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td><strong>Period of treatment (week)</strong></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Mean score</strong></td>
<td>9.9</td>
<td>6.5</td>
<td>7.6</td>
</tr>
<tr>
<td><strong>Difference % from week 0</strong></td>
<td>-</td>
<td>-38</td>
<td>-23</td>
</tr>
</tbody>
</table>

The more favourable evolution is seen in the dexchlorpheniramine group; the cetirizine group is not quite different from the placebo group.

As far as cetirizine is concerned, the reported results correspond to a mean dosage of 0.25 mg/kg à 0.07 n = 14.
In separating the patients of this cetirizine group in 2 subgroups, one receiving less than 0.25 mg/kg, the other receiving 0.25 mg/kg or more, we find (Table 2):

**TABLE 2**

<table>
<thead>
<tr>
<th>Mean scores in cetirizine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Number</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Period of treatment</td>
</tr>
<tr>
<td>Mean score</td>
</tr>
<tr>
<td>+ %</td>
</tr>
</tbody>
</table>

The analysis of the self assessment rating scale (from 0 to 10) was not possible because the scales were different at time 0 (continuous line) and at time 1 and 2 (scale graded from 0 to 10).
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 3.

**TABLE 3**

**Global evaluation**

<table>
<thead>
<tr>
<th></th>
<th>Cetirizine group</th>
<th>Placebo group</th>
<th>Dexchlorpheniramine group</th>
</tr>
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<tbody>
<tr>
<td>By the investigator</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 1</td>
<td>1.9 ± 1</td>
<td>1.6 ± 0.8</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.5 ± 1</td>
<td>1.9 ± 0.9</td>
<td>1.9 ± 1</td>
</tr>
<tr>
<td>By the patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>1.9 ± 1.2</td>
<td>1.9 ± 0.8</td>
<td>2.7 ± 1.2</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.7 ± 1</td>
<td>2.4 ± 0.9</td>
<td>2.2 ± 1.1</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.

**Side effects**

No side effects were reported.
IV. DISCUSSION

In this study, dextchlorpheniramine > placebo = cetirizine. When analysing separately the cetirizine group, with the posology referred to weight (mg/kg), it seems that the cetirizine activity is more evident when the dosage is sufficiently high. However, there is only a small difference with the placebo effect and in any case it is less than dextchlorpheniramine.

In addition to the problem of under-dosage for nearly half of the patients (and maybe too for the group of ≥ 0.25 mg/kg) the relative failure could be attributed to the once daily administration of cetirizine (cf. urinary cinetics of the child).

It is possible too that this study does not correspond to a full pollenic season, which might explain the good results obtained under placebo? (see Western Cape pollen calendar in appendix)

V. CONCLUSION

In the study conditions, no valuable conclusion can be drawn about the tested drugs.