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DOUBLE BLIND MULTICENTER STUDY OF THE SAFETY AND
EFFICACY OF CETIRIZINE IN THE TREATMENT OF
ASTHMA DUE TO POLLEN IN CHILDREN
(Protocol PCF88B102)

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DOUBLE BLIND MULTICENTER STUDY OF THE SAFETY AND EFFICACY OF CETIRIZINE IN THE TREATMENT OF ASTHMA DUE TO POLLEN IN CHILDREN

I. SUMMARY

The activity of cetirizine (0.2, 0.4 and 0.6 mg/kg/day) was studied in France in children suffering from grass pollen asthma. The study was a double blind study. The most reliable dosage was used so as to avoid early dropouts from the study due to uncontrolled rhinitis. The patients were allowed to use a β₂-mimetic by inhalation for asthma symptoms.

Fifty-one children entered the study for curative treatment, i.e. at the onset or relapse of asthma symptoms due to pollen. The duration of the study was 4 weeks.

Forty-seven case files were accepted for the analysis of efficacy, 16 in the 0.2 mg/kg/day (CET 2.5) group, 18 in the 0.4 mg/kg/day (CET 5) group and 13 in the 0.6 mg/kg/day (CET 7.5) group.

The symptoms of rhinoconjunctivitis were well controlled. None of the patients dropped out early due to uncontrolled rhinitis.

By the fourth week, there was a complete disappearance of the rhinoconjunctivitis symptoms in 4 patients in the CET 7.5 group, 6 patients in the CET 5 group and 2 patients in the CET 2.5 group.

As regards the asthma, by the fourth week there was a complete disappearance of symptoms in 4 patients in the CET 7.5 group, 9 patients in the CET 5 group and 6 patients in the CET 2.5 group.

One patient in the CET 7.5 group, 2 patients in the CET 5 group and 4 patients in the CET 2.5 group left the study prematurely due to ineffectiveness.

The efficacy index calculated on the basis of the daily cards (asthma score and β₂-mimetic consumption) and the premature dropouts from the study due to ineffectiveness suggests an advantage for the CET 5 and CET 7.5 groups vis-à-vis the 2.5 group as early as the third week of treatment. None of the observed differences reached the threshold of statistical significance.

The tolerance of the treatment was good. The incidence of sedative adverse effects seemed higher in the CET 7.5 group.
II. INTRODUCTION

Cetirizine is an active metabolite of hydroxyzine.

It is a powerful H1, selective antihistamine: at the 10 mg and 20 mg doses there are few sedative side effects (1,2). The antihistamine effect is of rapid onset and is characterized by its power and prolonged duration of action.

Cetirizine has recently been registered in most of the EEC countries for its action in the adult in seasonal and non-seasonal allergic rhinitis, urticaria and allergic pruritis (3, 4). Another interesting property is its inhibition of the bronchial constriction induced by histamine (5). It has also been shown to inhibit the migration of eosinophils in the skin after an allergic challenge (6). These properties led us to study the action of cetirizine in allergic asthma, both seasonal and non-seasonal.

Preliminary studies suggested a possible action of cetirizine at the dose of 10 mg 2 ×/day for this indication.
This study was conducted in France in the pollen season of 1988, with the aim of assessing the efficacy and tolerance of cetirizine, and in particular to answer the following two questions:

1) Is cetirizine active in asthma due to pollen in children?
2) Is cetirizine well tolerated at the dose used for this action?
III. MATERIAL AND METHODS

1. Organization of the Study

The study was conducted as a curative study, the children being included into the study on the development of symptoms of hay fever and asthma of recent onset.

Three dosages of cetirizine were used: 0.2 mg/kg/day (a dose active on the rhinitis and supposed not to have any effect on the asthma), 0.4 and 0.6 mg/kg/day (dosages investigated for their action on the asthma).

The duration of treatment was 4 weeks. Topical treatments, devoid of systemic effects, were permitted if control of the rhinitis necessitated this.
3. Selection of Patients

Children from both sexes were admitted into the study after their parents had given their informed consent. Their age had to be between 6-14 years. Their weight had to be over 20 kg. The patient’s allergy to pollen had to be documented either by a skin test or a positive RAST test for grass pollen. Patients presenting with non-seasonal, moderate asthma could be included into the study if they presented with a clear relapse of their asthma during the pollen season. Given the curative nature of the study, patients presenting with asthma due to pollen for the first time could also be included.

The allergic asthma had to be present for less than 96 hours on entry into the study and the patients should not have been treated with any other anti-asthmatic treatment other than a \( \beta_2 \)-mimetic by inhalation. On inclusion, the FEV1 had to be at least 70% of the previous value, with a reversibility on \( \beta_2 \)-mimetics of at least 15%.

The patient should not have received glucocorticoids systemically in the 6 weeks preceding inclusion, astemizole or cortico-steroids by inhalation during the 4 weeks preceding the study, theophylline, oral \( \beta_2 \)-mimetics, anticholinergic drugs, nasal topical cortico-steroids, inhaled chromoglycate or ketotifen during the 2 weeks preceding inclusion. Other antihistamine drugs were stopped on entry into the study.

Inclusion of patients into the study should start at the start of the grass pollen season in the region considered, confirmed by pollen counts during the course of the study.

The following children were excluded from the study: those with a past medical history of status asthmaticus, those suffering from another chronic respiratory disease, those taking any drugs likely to interfere with the assessment of the variables studied (sedatives, psychotropic drugs, anti-inflammatory agents, ...), those children presenting with an infection of the ENT system or the respiratory tract during the two weeks preceding inclusion.

Also excluded were patients who were suffering from hepatic, renal, or heart failure, those with allergy to the diphenylpiperazines, those likely to drop out from the study or not likely to respect its constraints.
4. Conduct of the Study

The patients were seen at two-week intervals, for a total duration of 4 weeks.

If the ENT symptoms were insufficiently controlled by the test drug, a topical treatment devoid of systemic effects could be prescribed, with the exclusion of a glucocorticoid for the first 2 weeks of the study.

Symptoms of asthma will be treated with a $\beta_2$-mimetic by inhalation, on demand, at the least required dose. If another anti-asthma drug is prescribed, the patient will leave the study for therapeutic ineffectivity. If a severe adverse event develops, the patient will also leave the study.

5. Variables Measured

At each medical visit, the investigator takes a history regarding the patient's general complaints, the rhinoconjunctivitis and asthma, and makes a clinical assessment of the ENT and respiratory symptoms. He also obtains from the patient an appreciation of his own condition using two visual graduated analogical scales, one for the rhinoconjunctivitis, the other for the asthma. At the second visit, the doctor also notes any information regarding associated drugs or possible adverse effects. Every day at home the patient fills out a report in which he states his nocturnal and diurnal asthma symptoms (4-point scale), his values for his peak expiratory flow in the morning and the evening (the best of 3 attempts), his consumption of $\beta_2$-mimetics in the morning and the evening and any special events which have occurred during the day.
6. Statistical Analysis

A global evaluation of the efficacy of treatment was conducted every week, using a scoring system from 0 to 6, taking into account the symptoms and the use of fall-back medication ($\beta_2$-mimetics), using the following calculation:

\[
\text{mean daily asthma score + mean score of } \beta_2\text{-mimetic consumption, in which:}
\]

\[-\text{ mean daily asthma score} = (\text{mean nocturnal asthma score} + \text{mean diurnal asthma score})/2\]

\[-\text{ mean score of } \beta_2\text{-mimetic consumption:}\]

<table>
<thead>
<tr>
<th>Consumption</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No consumption</td>
<td>0</td>
</tr>
<tr>
<td>Less than 2 puffs/day</td>
<td>1</td>
</tr>
<tr>
<td>Between 2 and 6 puffs/day</td>
<td>2</td>
</tr>
<tr>
<td>More than 6 puffs/day</td>
<td>3</td>
</tr>
</tbody>
</table>

If the patient leaves the study due to ineffectiveness, a score of 6 is arbitrarily attributed at the time of interruption.

A higher score therefore corresponds to more severe asthma symptoms and/or greater use of fall-back medication and consequently, lower efficacy of the test drug.

The statistical analysis involved mainly the comparison of these scores in the various therapeutic groups.

The smallest clinically pertinent mean difference is considered to be equal to one unit of this index.
At the end of the treatment, the therapeutic groups were compared on the basis of the global evaluation of the investigator and the patient himself.
Given that there were 3 therapeutic groups, the following analyses were conducted:

- a global comparison of the 3 groups
- a paired comparison:
  - CET 5 vs CET 2.5
  - CET 7.5 vs CET 2.5
  - CET 7.5 vs CET 5

For the global comparison of the 3 groups, the comparison of the distribution frequency of symptoms at each visit used the chi-squared test. For the visual analogical scales, the Kuskall-Wallis test was used (on the differences, when a baseline was available). For the index of efficacy and the variables on the daily cards, the same test was used, except for the peak flow rates for which a one criterion variance analysis was used.

For the 2 by 2 comparisons, the comparison of the distribution frequency of symptoms, stratified in relation to the baseline, used the following 2 tests: the stratified chi-squared test of Cochran-Mantel-Haenszel for the comparison of the treatments, and the Breslow-Day test for the analysis of the interaction treatment x strata. For the visual analogical scales, the Wilcoxon rank test was used (on the differences, when a baseline was available). For the efficacy index and the variables on the daily cards, the same test was used, except for the peak flow rates for which Student's t-test was used.

For the adverse events, we used the chi-squared test for the global comparison, and the exact test of Fisher for the 2 by 2 comparisons.

The threshold of statistical significance accepted was 5%.
IV. RESULTS

1. Population

A total of 51 patients were included in 7 centers (Appendix 1).

These patients were comparable regarding their age, weight, height, sex and past medical history of allergic asthma (Table I). Forty-one of these 51 children were aged between 5 and 12 years.
2. Efficacy

A. Symptoms of rhinoconjunctivitis (Table II)

- conjunctivitis

Nine of the 15 patients in the CET 2.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 6 and 6.

Fifteen of the 17 patients in the CET 5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 6 and 9.

Ten of the 13 patients in the CET 7.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 6 and 5.

There was no statistically significant difference between the groups.

- nasal obstruction

Twelve of the 15 patients in the CET 2.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 11 and 10.

All 17 patients in the CET 5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 10 and 10.

All 13 patients in the CET 7.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 8 and 6.

There was no statistically significant difference between the groups. Note that these three groups were not initially comparable for this symptom (p = 0.04).

- rhinorrhea

Fourteen of the 15 patients in the CET 2.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 11 and 10.

All 17 patients in the CET 5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 13 and 8.
Twelve of the 13 patients in the CET 7.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 7 and 4.

Group CET 7.5 shows a tendency to a better evolution at the final visit than Group CET 5 (p = 0.06).

- sneezing

Fourteen of the 15 patients in the CET 2.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 10 and 6.

All 17 patients in the CET 5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 9 and 6.

Twelve of the 13 patients in the CET 7.5 group presented with the symptom on inclusion; On the second and final visits, these numbers were 7 and 4.

There was no statistically significant difference between the groups.

- global evolution of the rhinoconjunctivitis

If we group together these 4 symptoms of hay fever and we analyze the number of patients in whom the symptoms disappeared, the following results were obtained.

Fourteen of the 15 patients in the CET 2.5 group presented with at least one symptom on inclusion. On the second and final visits, 14 and 12 of these patients remained symptomatic. The remaining patient later became symptomatic.

All 17 patients in the CET 5 group presented with at least one symptom on inclusion. On the second and final visits, 15 and 11 of the patients remained symptomatic.

All 13 patients in the CET 7.5 group presented with at least one symptom on inclusion; On the second and final visits, 10 and 9 of these patients remained symptomatic.

Group CET 7.5 shows a tendency to a better evolution than Group CET 2.5 at visit 2 (p = 0.06).
B. Symptoms of Asthma: (Table III)

- wheezing

Fourteen of the 15 patients in the CET 2.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 9 and 7.

Sixteen of the 17 patients in the CET 5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 10 and 7.

Ten of the 13 patients in the CET 7.5 group presented with the symptom on inclusion; On the second and final visits, these numbers were 6 and 6.

There was no statistically significant difference between the groups.

- dyspnea

Nine of the 15 patients in the CET 2.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 7 and 6.

Sixteen of the 17 patients in the CET 5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 11 and 6.

Seven of the 13 patients in the CET 7.5 group presented with the symptom on inclusion; On the second and final visits, these numbers were 8 and 6.

There was no statistically significant difference between the groups. It should be pointed out that the three groups were initially not comparable for this symptom (p = 0.03).

- cough

All 15 patients in the CET 2.5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 10 and 6.

All 17 patients in the CET 5 group presented with the symptom on inclusion. On the second and final visits, these numbers were 9 and 6.

All 13 patients in the CET 7.5 group presented with the symptom on inclusion; On the second and final visits, these numbers were 8 and 9.
There was no statistically significant difference between the groups. The CET 7.5 group showed a poorer evolution than the CET 5 group for this symptom (p = 0.07).

- **Global evolution of the asthma**

When the 3 symptoms of asthma are taken together and we analyze the number of patients in whom these symptoms disappeared, the following results are obtained.

All the 15 patients in the CET 2.5 group presented with at least one symptom on inclusion. On the second and final visits, 12 and 9 of these patients remained symptomatic.

All 17 patients in the CET 5 group presented with at least one symptom on inclusion. On the second and final visits, 14 and 8 of the patients remained symptomatic.

All 13 patients of the control group presented with at least one symptom on inclusion. On the second and final visits, 9 and 9 of these patients remained symptomatic.

There was no statistically significant difference between the groups.

C. Autoevaluation of the Patients (Table IV)

The visual analogical scales for the symptoms of rhinoconjunctivitis show a mean initial score of 48 mm in the CET 2.5 group, 36 mm in the CET 5 group, and 42 mm in the CET 7.5 group.

At the second and final visits, these values increase to 16 and 21 mm for the CET 2.5 group, 32 and 34 mm for the CET 5 group and 29 and 33 mm for the CET 7.5 group.

The visual analogical scales for asthma show a mean initial value of 48 mm for the CET 2.5 group, 39 mm for the CET 5 group, and 44 mm for the CET 7.5 group.

At the second and final visits, these values increase to 24 and 26 mm for the CET 2.5 group, 30 and 36 mm for the CET 5 group, and 30 and 34 for the CET 7.5 group.
There was no statistically significant difference between the three groups.

D. Global Evaluations at the End of the Study (Table V)

- **Symptoms of rhinoconjunctivitis**

  The global evaluation of efficacy both by the investigator and the patient showed similar overall results for the 3 groups.

- **Symptoms of asthma**

  The global evaluation of efficacy both by the investigator and the patient showed a fairly similar result in all the 3 groups.

E. Examination of the Daily Cards:

- **Peak Expiratory Flow Rate: (Table VI)**

  The peak expiratory flow rate in the morning and the evening improved very slightly in the 3 therapeutic groups.

- **Asthma scores: (Table VII)**

  The mean initial asthma scores were fairly low: 0.4 at night and 0.8 during the day. The nocturnal score improved more with treatment CET 7.5. This difference is nevertheless not statistically significant.

- **Consumption of $\beta_2$-mimetics: (Table VIII)**

  The initial $\beta_2$-mimetic consumption was low to moderate (on average 1.9 puffs/day during the course of the first two days).

  This consumption fell by more in the CET 7.5 group, than in the other two groups.

  This difference was nevertheless not statistically significant.
F. Efficacy Index: (Table IX)

The efficacy index which took into account asthma scores, the consumption of β₂-mimetics and the dropout rate from the study for ineffectiveness shows the following differences vis-à-vis the CET 2.5 group:

<table>
<thead>
<tr>
<th>for the CET 5 group</th>
<th>for the CET 7.5 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 1: - 0.2</td>
<td>week 1: 0.1</td>
</tr>
<tr>
<td>2: 0</td>
<td>2: 0.2</td>
</tr>
<tr>
<td>3: 0.5</td>
<td>3: 0.5</td>
</tr>
<tr>
<td>4: 0.4</td>
<td>4: 0.6</td>
</tr>
</tbody>
</table>

The CET 5 and CET 7.5 groups therefore had a tendency to a better evolution by the third week. The difference in the index nevertheless did not reach unity and none of the differences reached the threshold of statistical significance.

G. The Use of Supplementary Treatments for Rhinoconjunctivitis

One patient in the CET 2.5 group and 2 patients in the CET 5 group had to fall back on a supplementary treatment for the rhinoconjunctivitis symptoms.
3. Tolerance (Table X)

Thirteen patients reported adverse events, 4 of the 17 patients of the CET 2.5 group, 3 of the 17 patients of the CET 5 group and 6 of the 15 patients of the CET 7.5 group. Neurological sedative effects were the most frequently reported: they were reported by 1 patient in the CET 2.5 and CET 5 groups and 5 patients in the CET 7.5 group. The incidence of sedative effects therefore seems to increase with an increase in the dose of cetirizine. The number of cases is however insufficient to be able to draw definitive conclusions.

The other neurological effects (excitation, vertigo) were not very frequent. Note an increase in appetite in two children.
V. DISCUSSION

The 1988 pollen season extended more or less from the end of April to the end of July, with the peak pollen count being extremely variable depending on the region considered, falling generally around the end of May and the beginning of June. Most of the patients were included in two or three successive waves, often corresponding to an increase in the grass pollen count to a maximum and a second later peak. For one center (St. Pons), we do not have data for the pollen count, and for the second center (Clermont-Ferrand), we only have fragmentary data. The inclusion period for these two centers was nevertheless within the same time frame of inclusions for the other centers, except for one case at St. Pons (150/02), who was included much later (at the end of July).
Given the small number of patients (13 to 17 per therapeutic group), the results have to be analyzed with some care. A center by center analysis was not possible because of the disproportionate number of cases in the centers: the Lyon/Valence center alone supplied half the total population.
The tolerance of cetirizine at these 3 doses was in general good. It should be pointed out, however, that the incidence of sedative effects seems to increase with the dose, although the number of patients treated was insufficient to draw any definitive conclusions. Only 1 child in the CET 7.5 group had to leave the study due to somnolence induced by the drug. A relationship between the other adverse events which led to
premature interruption of the study and the test drug cetirizine was not established. The case of Quincke’s oedema occurred in the third week of treatment when the child changed his environment (walk in a grassy area); the investigator attributed the adverse event to this change in the environment.

VI. CONCLUSION

The small number of patients included in the study do not allow any definite conclusions to be drawn regarding the activity of cetirizine in asthma due to pollen in children.

The highest dosage used (0.6 mg/kg/day) would be the recommended dose for further studies in this indication. It seems to be the most effective dose and seems in general to be well tolerated. One case of Quincke’s oedema occurred during the course of the study but a relationship of cause and effect with cetirizine was not established.
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