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A DOUBLE-BLIND, MULTICENTER STUDY OVER 2 WEEKS OF CETIRIZINE (one 10 mg tablet omni nocte) VERSUS PLACEBO IN THE TREATMENT OF ALLERGIC RHINITIS IN CHILDREN AGED BETWEEN 6 AND 12 YEARS (protocol PCF88L222)

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SUMMARY

Thirty-eight patients, aged between 6 and 12 years and suffering from allergic rhinitis, were recruited by 5 investigators to take part in a double-blind study designed to compare the activity of cetirizine versus placebo.

Every day, each patient was given one 10 mg tablet of cetirizine, or an identical tablet of placebo, with the evening meal, for between 14 and 20 consecutive days.

At three visits — before, after 1 week, and after two weeks of treatment — the investigator evaluated the symptoms (sneezing — rhinorrhea — nasal congestion — nasal pruritus — ocular pruritus), using a 4-point scale, in which 0 = no symptoms and 3 = severe symptoms.

At the end of the treatment, the investigator gave a global appreciation of the action of the test product using a 5-point scale: from 0 = aggravation to 4 = excellent improvement.

The patients themselves, or their parents, filled a daily auto-evaluation card every evening, in which they assessed the following symptoms: sneezing — runny nose — blocked nose — irritation in the nose — irritation of the eyes. Any special events that occurred concerning the study were also noted, as well as any other drugs taken.

The safety of the test treatment was assessed on the basis of the adverse effects noted, and laboratory tests conducted before and at the end of the study.

Thirty four children (13 girls and 21 boys) were retained for the analysis of efficacy. Cetirizine had a superior action to that of placebo on all the symptoms. However, this superiority reached statistical significance only for nasal obstruction (p = 0.008) and the global score for the symptoms of rhino-conjunctivitis (p = 0.032), as evaluated by the investigator after the first week of treatment. The superiority of cetirizine also reached statistical significance for the sneezing, as evaluated by the patients (or the parents) after the second week of treatment. The fall in the global score of the rhino-conjunctivitis symptoms and the ocular pruritus, as evaluated by the investigator after the second week of treatment, was close to statistical significance (p < 0.1). The clinical tolerance was excellent and the laboratory tests were normal.
I. INTRODUCTION

A pharmacokinetic study conducted in children aged between 6 and 12 years receiving cetirizine for their allergic rhinitis demonstrated that the plasma half-life of this antihistamine was around 6 hours in this age group (1), whereas it was 9 hours in adults (2).

For this reason, in the first pediatric studies conducted with this molecule, cetirizine was given in two doses per day, in the morning and evening, to children aged between 6 and 12 years (3-4-5).

A later study (6), also conducted in children aged between 6 and 12 years suffering from allergic rhinitis, did not show any clinically significant difference between cetirizine given in a single daily dose of 10 mg, or in 2 divided doses of 5 mg per day.

The object of the present study was to confirm that cetirizine is both effective and well tolerated when it is given in a single dose of 10 mg to children aged between 6 and 12 years suffering from allergic rhinitis.
II. **METHOD**

1. **Design of the study**
   We had to compare, in a random and double-blind study, 10 mg of cetirizine versus a placebo, administered for 2 weeks to 2 parallel groups of 40 patients aged between 6 and 12 years and suffering from allergic rhinitis.
The patients included in the study were children aged between 6 and 12 years, presenting with allergic rhinitis due to pollen, which was well documented either by the history (diagnosis made at least 1 year previously) or by at least one positive allergy test for pollen at the time of inclusion (skin test or RAST test - possibly nasal provocation test).

The patients had to show at least 3 of the following symptoms: sneezing -- rhinorrhea -- nasal congestion -- nasal pruritus -- ocular pruritus. The severity of the condition had to be such that the sum of the scores for these five symptoms, as measured on a 4-point scale (0 = absent, 1 = mild, i.e., present but not troublesome, 2 = moderate, i.e., troublesome but not interfering with daytime activities or sleep, 3 = severe, i.e., disturbing daytime activities or sleep), was equal to or greater than 8.

The children could be included even if they were suffering from another allergic condition (nonseasonal rhinitis, atopic dermatitis, or asthma) but the condition could not be in an evolutionary phase, i.e., requiring a change in the normal treatment at the time of inclusion.

Patients with vaso-motor or infectious rhinitis, nasal polyps, infection of the upper respiratory tract in the 3 preceding weeks, and in general any infection requiring antibiotic treatment, were excluded from the study.

Patients allergic to the piperazines, including hydroxyzine and cetirizine, were excluded from the study, as were those with clinically significant renal, hepatic or cardiovascular disease, or any other condition, including clinically significant lab test abnormalities which might interfere with the clinical study.
On inclusion into the study, the children were no longer permitted antihistamines, decongestants, sedatives, or topical, nasal or ocular preparations.

The following drug-free intervals had to be respected if the patients had previously been receiving any of these treatments: 4 weeks for astemizole, 2 weeks for systemic corticosteroids and for ketotifen, 1 week for nasal or ocular corticosteroids and disodium cromoglycate, 2 days for decongestants and oral antihistamines other than astemizole or ketotifen. However, the following drugs were permitted if the patient was being treated for asthma: theophylline, β2-mimetics, inhaled disodium cromoglycate, nedocromil, and inhaled corticosteroids, as long as the daily dose did not exceed 200 μg. Non-steroid local treatment for atopic dermatitis was also permitted.

If the patient was undergoing desensitization treatment, this was permitted as long as the treatment was not in the ascending phase.

Patients who had recently changed their environment were not accepted into the study, nor were subjects who were likely to move house, leave on weekends or holidays, etc. during the period of the study. Subjects who seemed to be insufficiently reliable were also not included into the study.

If the subject had participated in another therapeutic trial in the 3 preceding months, he or she was not included into the study.

3. **The test treatments**
   Every day, with the evening meal, for 14 to 20 consecutive days, in two periods of between 7 and 10 days, each patient received a tablet of 10 mg of cetirizine or an identical tablet of placebo.

   A certain number of concomitant drugs were permitted during the study, others were forbidden, and some had to be discontinued for a specified period (see II.2).

4. **Conduct of the study**
   Three visits were required for each patient: visit 1, the inclusion visit, on D1; visit 2, a control visit between D7 and D10; and visit 3, the final visit, between D14 and D20.
5. **Evaluation of efficacy**
   The efficacy was evaluated on the basis of the symptoms of rhinitis as measured at each visit, the global evaluation at the last visit, and the daily record cards completed by the patients.

6. **Evaluation of the safety**
   The safety was evaluated on the basis of the laboratory tests before and after the treatment (with the exception of the Clermont-Ferrand center, where the blood tests were not permitted by the Ethics Committee), and the adverse events noted at the control visits.
7. **Statistical methods**

The methods used were those generally used for the comparison of two independent groups. These comparisons were conducted:

- on the variables recorded at each visit by the investigator: the last visit was visit 3 for those patients who completed the course of treatment, and visit 2 for those who interrupted treatment early.
- for the variables noted by the patient on the daily evaluation cards, using the means calculated for each treatment period. When a patient interrupted treatment prematurely for inefficacy, the mean obtained for the period preceding interruption was used for the second period.

Whenever a baseline was available, this was used in the comparisons in the following manner:

- in the variables obtained at the visits to the investigator, the baseline was taken to be the data collected at the first visit.
- for the variables of the daily evaluation cards, the baseline was taken as the mean of the day preceding visit 1, and the day of visit 1 itself.

All the tests were bilateral tests with a threshold of significance of 5%. The statistical analysis is shown in report CE90C062.

a) **Symptoms**

A statistical analysis was conducted for each symptom separately, and for the global score, defined as the mean of the 5 symptoms for each patient. For each symptom and for the global score, we have a statistical summary by treatment group for each visit, and for the differences as compared to the baseline. A Wilcoxon test conducted on the differences from the baseline values compared the two treatment groups.

b) **Global evaluation of the treatment**

A statistical summary was made for each treatment group, and a Wilcoxon test was conducted to compare the two treatment groups.

c) **Daily evaluation cards**

A statistical summary is given by treatment group and by period on the differences as compared to the baseline. A Wilcoxon test conducted on the differences as compared to the baseline compared the two groups.

d) **Adverse events**

These were classified according to the COSTART method, and Fisher's exact test was used to compare the proportion of patients who presented with one or more adverse events.
III. **RESULTS**

1. **Demographic data**
   Five centres participated in the study to varying degrees (see table 1).
The two groups were comparable from the point of view of their sex distribution, age, weight, height and length of illness (see table II). Furthermore, the severity of the condition was not different in the two groups at the time of inclusion into the study (see table III). The compliance with the treatment was satisfactory in all the patients who were included in the analysis of efficacy.

2. **Analysis of efficacy**

   a) **Evaluation by the investigator at the various visits.** (figures 1 to 6)

   If we examine the changes in the symptoms as evaluated at each visit by the investigator (scale from 0 to 3) there is an improvement in the symptoms in both groups of patients, but the improvement is more marked in the cetirizine group (see table IV).

   There is a statistically significant difference in favor of cetirizine for nasal congestion ($p = 0.008$) and for the global score ($p = 0.032$) after the first week of treatment.

   For this latter parameter, a similar tendency is seen after the second week of treatment ($p = 0.067$); this is also true for ocular pruritus ($p = 0.089$). This better activity of cetirizine is seen in the global evaluation, by the investigator, of the treatment effect. This is confirmed by the fact that 2/3 of the patients on cetirizine were improved, whereas more than 1/2 of the patients on placebo were little or not at all improved (see table V).
b) **Autoevaluation of the symptoms by the patient**

For most of the symptoms, the greatest improvement was seen with cetirizine. Nevertheless, on a scale from 0 to 3, this improvement is significant only for sneezing after the second week of treatment (p = 0.045) (see table VI).

3. **Analysis of safety**

a) **Adverse events**

Four adverse events were reported, 3 on cetirizine and 1 on placebo (see table VII).

- In patient 368/02 (cetirizine), who complained of a disagreeable taste in the mouth, the investigator was unable to ascertain whether the patient was not chewing the tablets; this complaint persisted throughout the length of the study.

- The hyperthermia seen in patient 371/01 (cetirizine), which appeared on days D8 and D9, was considered to be a single episode of moderate severity, attributable according to the investigator, to the rhinitis itself, and it did not require any change in the treatment. A short course of symptomatic treatment led to the disappearance of this episode of hyperthermia.

- Patient 371/03 (cetirizine) complained of glossitis (between D10 and D15) and perleche (between D10 and D19), which were judged to be mild and possibly related to the treatment. They did not require any specific treatment, and did not affect the conduct of the study.

Patient number 371/06 (placebo) complained of gastric pain which appeared 6 days after the beginning of treatment. The pain was still persistent at the end of the study. It was intermittent, moderately severe and judged to be possibly related to the test treatment, but not requiring any specific treatment or change in the course of the study.

b) **Laboratory tests**

No laboratory tests were conducted on the 7 patients under investigator n° 368 (objection of the Ethics Committee). Patient 369/01 was also not investigated (laboratory error !).

In patient 371/05, only the laboratory test results before treatment are available, because the study was abandoned after only 2 days of treatment, for reasons not related to the study itself. In this patient, a certain number of abnormalities were observed: hematocrit 32 % (normal between 37 to 45 %); lymphocytes 55 % (normal between 25 and 40 %); and alkaline phosphatase 454 1.U./l (normal between 60 and 170 1.U./l). These abnormalities were not thought remarkable by the investigator, who included the patient into the study.
The changes in the liver function tests in each of the two groups were as follows:
- in the cetirizine group: the SGOT concentration increased in 6 cases, fell in 6 cases, and remained unchanged in 2 cases.
  the SGPT concentration increased in 8 cases, fell in 4 cases, and remained unchanged in 2 cases.
- in the placebo group, the figures were, respectively, 7, 6 and 1 (SGOT) and 5, 9 and 0 (SGPT).

4. **Pollen counts** (appendix 2)
If we look at the curves of the pollen counts, we note that in some patients there was no correlation between the pollen count and the symptoms.
IV. DISCUSSION

An initial calculation of the numbers required for this study suggested that a total of eighty patients was necessary, forty in each of the two treatment groups. Each centre had to recruit twenty patients.

Despite the addition of a fifth centre, the total number of patients which could be recruited into the study during the pollen season of 1989 was only thirty-eight, a figure less than one half of the number required.

The curves of the pollen count showed that in the regions in which the study was conducted, the peaks for grass pollen were short and low (St. Etienne for Clermont Ferrand, Montpellier, Lyon) or practically absent (Perpignan, Marseille for Aix-en-Provence) in the period of the study, between the end of March and the end of July. Instead, in this year of 1989, there was a high concentration of cypress pollen by January and February in the south of France, before the study had been set up. Subsequent changes in the climate, which became very hot and dry, prevented the development of a high grass pollen count. This was especially the case in Perpignan.

Despite these unfavorable conditions for demonstrating a therapeutic effect, the improvement in the symptoms was more evident in the patients who received cetirizine. This difference was seen especially by the investigator for the symptom of nasal congestion; on a 0 to 3 scale this fell by 1.4 points on cetirizine versus 0.3 points on placebo, after 1 week of treatment. The efficacy of treatment was also seen in the global score of rhino-conjunctivitis symptoms, which fell after 1 week by 1.3 points on cetirizine and by 0.9 points on placebo.

From the point of view of safety, adverse effects were rare and benign, and there were no significant abnormalities in the blood tests. However, in two patients receiving cetirizine, the SGOT increased slightly beyond the upper limit of normal for the laboratory, at the end of the treatment. However, an overall examination of the changes in the liver-function tests of the two groups does not show any significant difference.
v. CONCLUSION

Even though this study was conducted in conditions unfavorable for the demonstration of a therapeutic action, cetirizine proved to be more effective than placebo in this small sample of patients suffering from allergic rhinitis. The drug was well tolerated clinically, and the laboratory tests were normal. No cases of sedation were reported.
REFERENCES

1. **Report DE89A202**
   Clinical pharmacokinetics of cetirizine 5 mg p.o. in pediatric patients with allergic rhinitis.

2. **Baltes E.L.**
   Pharmacokinetics of cetirizine in animal species and in man.

3. **Report CF88L031**
   Etude de l’efficacité et de la tolérance de différentes doses de cétirizine dans la pathologie allergique de l’enfant d’âge scolaire souffrant de rhinite allergique: comparaison, en double insu, de 2 doses de cétirizine (2 x 2.5 mg/d et 2 x 5 mg/d) à un placebo, dans 3 groupes parallèles traités pendant 2 semaines.

4. **Report CF88M083**
   Etude multicentrique comparant la cétirizine à la terfenadine chez des enfants de 6 à 12 ans présentant une affection allergique.

5. **Report CF89A131**
   Etude multicentrique, en double insu, sur groupes indépendants, de la cétirizine, 10 mg/d pendant 4 semaines, comparée au placebo dans le traitement de la rhinite pollinique chez l’enfant de 6 à 12 ans.

6. **Report CF88J141**
   Etude multicentrique de l’efficacité et de la sécurité d’emploi de la cétirizine administrée en 1 ou en 2 prises journalières à des enfants de 6 à 12 ans atteints de rhinite saisonnière. Comparaison à la terfenadine.