STUDY OF THE EFFICACY AND TOLERANCE OF DIFFERENT DOSES OF CETIRIZINE
IN ALLERGIC CONDITIONS IN 6 TO 12-YEAR OLD CHILDREN
SUFFERING FROM CHRONIC ALLERGIC RHINITIS

A double blind comparative study of two doses of cetirizine
(2.5 mg bd and 5 mg bd) and placebo
in 3 parallel groups treated for 2 weeks
(Protocol PCE87A153)

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SUMMARY

Cetirizine, given at two different doses, 2.5 mg bd and 5 mg bd, was compared to a placebo, in three groups of 46 patients aged from 6 to 12 years and suffering from perennial allergic rhinitis.

The treatment was given for a two-week period and the patients assessed after the first, and again after the second week of treatment.

The parameters chosen for evaluation of efficacy of the test substance were nasal obstruction, non-purulent rhinorrhoea, nasal pruritis, sneezing and pharyngeal drips. In addition to these main symptoms, the secondary symptoms studied included a sore throat, conjunctival erythema, lacrimation, ocular pruritis and, in addition, the presence or absence of a cough.

Each of these symptoms was assessed using a scale graduated from 0 = "none" to 4 = "very severe", the latter requiring additional medication for control of the symptoms, and this in itself constituting one of the exclusion criteria.

To be included in the trial, the patients must have had a global score of more than 10 out of a possible 27.

Treatment tolerance was assessed on the basis of any adverse events observed during the course of treatment, together with the results of the blood tests carried out prior to starting treatment and again upon completion of the study.

For his part the patient had to record on a daily basis the severity of his symptoms and assess his tolerance of the treatment received.

Both groups on cetirizine showed a greater improvement than the placebo group and the greatest improvement was seen in the 10 mg daily cetirizine group. This dose would seem to be the dose of choice for the treatment of symptoms of perennial allergic rhinitis, including nasal obstruction.

At this dose, tolerance was considered excellent.
I. INTRODUCTION

Cetirizine HCl has been shown, in both animal and human pharmacology studies, to be a potent antihistamine which is devoid of any anticholinergic effect at normal therapeutic doses.

In adults, cetirizine was shown to be effective in the treatment of rhinitis and urticaria, classically the action of an antihistamine but which, in this case, was rarely accompanied by sedation (refs. 1 - 6). It therefore appeared interesting to study cetirizine in allergic children, who often have problems at school with standard treatment because of the sedation produced.

We chose to look at chronic rhinitis in children aged from 6 to 12 years in this study, which was set out to determine the effective and well tolerated dose.
II. MATERIAL AND METHODS

1) Two different doses of cetirizine - 5 & 10 mg/day - were compared to placebo within the design of a double-blind, multicentre study with three independent groups of patients.

2) At each centre, according to a randomisation list, the patients were allocated to one of the three following treatment groups:
   - cetirizine: 1 tablet (2.5 mg) morning and evening (batches 66 & 68).
   - cetirizine: 1 tablet (5 mg) morning and evening (batches 67, 72 and 80).
   - placebo: 1 tablet morning and evening (batches 62P, 73P and 93P).
All the tablets were identical in taste, shape and form.

3) Treatment was given for a two-week period and the study was to last two to three months.

4) A minimum of 60 patients was required for analysis, this number to be distributed in groups of 9 to 12 among the centres in Germany, Belgium, France and the Netherlands.

5) The study was carried out in accordance with the terms of the Helsinki agreement. The protocol was submitted to the Ethical Committees for the Emma Kinderziekenhuis, Amsterdam and for the Hospital of Braine l'Alleud-Waterloo, for their approval, which was duly accorded. The informed consent of the parents was required and, to this end, they were given full details as to the procedures involved and received a full assurance that they could withdraw their offspring from the study at any time.

6) Girls and boys aged from 6 to 12 years, suffering from chronic allergic rhinitis for at least two years were selected to take part. Their allergic condition had to be well documented and supported by specific tests, (skin tests and/or RAST) to allergens other than pollen, with a mention of any antihistamine therapy and the outcome of the later. At least two of the principal symptoms of a chronic allergic rhinitis had to be present, i.e. two of the five detailed below:
   - nasal obstruction
   - non-purulent rhinorrhea
   - nasal pruritus
   - sneezing
   - pharyngeal drips
The following symptoms were also evaluated:
- sore throat
- conjunctival erythema
- lacrimation
- ocular pruritis.

The investigator calculated the total score, using a five-points scale graded from 0 = no symptoms to 4 = very severe and requiring the use of another medication than antihistamine. To be included, the patients had to have a total score greater than 10 out of a maximum 27 (9 symptoms graded each as 3 points), score 4 for one symptom being an exclusion criterion.

The children could also suffer from other allergic conditions such as pollinic rhinitis or atopic dermatitis but, in these cases, they could not receive another treatment than the study drug. In asthmatic patients, for whom the symptom of "cough" was also graded on a scale of 0 to 4, the only additional medication permitted was Na Cromoglycate or inhaled β₂-mimetics, or corticosteroids to a maximum dose of 400 μg/day by inhalation.

Children suffering from a non-allergic rhinitis, URTI, acute sinusitis or otitis media, a non-allergic nasal obstruction, any infection requiring antibiotics, a known allergy to piperazines, any chronic condition capable of interfering with the study, immune therapy over the course of the preceding year, under weight or obesity, malabsorption, parasitic infestation or abnormal blood tests were excluded from the study.

Participation in another drug trial within the six months prior to the study, or some changes in their environment, e.g. moving house, domestic pets, also constituted criteria of exclusion.

A "wash-out" period of varying duration was imposed prior to the patient’s inclusion in the study. Details are given below:

1 week for oral corticosteroids
  antibiotics
  decongestants
  antihistamines other than astemizole.
1 month for astemizole and depot corticosteroids.

Throughout the course of the study, antihistamines other than the test product, corticosteroids, anticholinergics, sedatives, adrenergic drugs, anti-inflammatory drugs and aspirin in particular were prohibited.
7) The investigator had to see the patient on four occasions during the study
III. RESULTS

The study took place from April 13, 1987 to February 10, 1988. 17 investigators took part (v. App. I), distributed as follows:

- Germany - 3 investigators for 29 patients
- Belgium - 12 investigators for 89 patients.
- France - 1 investigator for 2 patients.
- Netherlands - 1 investigator for 18 patients.

The results were subjected to statistical analysis and the findings are to be found in Report No CE88J162*

A. General information

138 patients, divided into three groups of 46, were included.
6. Statistical methods and analysis

The following tests were employed:

- Kruskal-Wallis test to compare the three groups
- Wilcoxon test for pairwise comparison
- Regression analysis to study the influence of age and dosage regime on the results obtained after treatment.

A mean score was calculated for each patient from Day 3 to Day 14 of treatment, in order to permit analysis of the Daily Record Cards which had been completed by the parents.

B. Patient Details

A total of 138 files were received from 46 girls and 92 boys aged from 2 to 14, all suffering from chronic rhinitis for a period varying from one to ten years. No difference as to these parameters was evident among the three groups, nor relative to weight or height. The mean global scores calculated at the time of their inclusion in the study were also comparable for the three groups (v. Table 1).
C. Efficacy

The analysis of efficacy included data obtained at visit 2 (the inclusion visit) or at visit 1 (the selection visit) for those patients who, in accordance with the terms of the protocol, had had only one visit, this serving as a baseline reference: they were 102 patients in this situation. As a great many patients (25) had not complied with the controls imposed at visit 3, only the data obtained at visit 4 (or at visit 3 for those who did not attend for visit 4), was taken into consideration.

1. The Wilcoxon test, employed for analysis of the change in symptoms as seen by the Investigator, clearly demonstrated (v. Table 2) a greater improvement in the scores

   - in the 5 mg bd cetirizine group than in the placebo group as regards nasal obstruction (p=0.03) and rhinorhoea (p=0.03).

   - in the 5 mg bd cetirizine group than in the 2.5 mg bd cetirizine group as regards pharyngeal drips (p=0.03)

   - in the 2.5 mg bd cetirizine group than in the placebo group as regards sneezing (p=0.04).

Analysis of the global score (v. Table 3), applying the Wilcoxon test, based on the mean of the scores obtained for each of the five principal symptoms and the four secondary symptoms, confirms the superiority of the 5 mg bd cetirizine group over placebo (p=0.01).

   - the 5 mg bd dose of cetirizine was shown on global evaluation of efficacy (v. Table 4) to be clearly superior to both placebo and the 2.5 mg bd dose of cetirizine (p= 0.04).

2. When the parents had to evaluate the symptoms of their children, the 5 mg bd cetirizine group emerged as significantly better than the two other groups with regard to "sore throat" only (p=0.05) (v. Table 5).

   It should be borne in mind that in order to avoid the variations associated with the time of starting of the study, the analysis only took into consideration data obtained from Day 3 to Day 14.

3. The visual analogue scales to be completed by the young patients were, as had been feared, very seldom correctly done and in the majority of cases not completed at all. For this reason, these results were not taken into account for analysis.

D. Dose-related effect

Analysis of regression demonstrated a significant dose-effect relationship for nasal obstruction only. The first therapeutic dose appears to be in the region of 0.25 mg/kg.

No dose-related effect was seen for any of the other symptoms.
E. Safety

Some side effects were reported from each of the three groups but these were less frequent in the 5 mg bd cetirizine group: three patients compared to eight in the 2.5 mg bd cetirizine group, and to six in the placebo group (v. Table 6).

Sedation was reported especially by:
- 2 patients in the 5 mg bd cetirizine group
- 4 patients in the 2.5 mg bd cetirizine group
- 3 patients in the placebo group
They described their symptoms as "tiredness", "calm", "sleepiness", "difficulty in waking".

An increase in appetite was noted for one patient in the 5 mg bd cetirizine group and for one patient in the 2.5 mg bd cetirizine group.

Gastrointestinal problems, such as abdominal pain and diarrhoea, were noted in one patient from each of the three groups.

Haematology and biochemistry (v. App. III) was not done for all patients and, in some cases, was done only prior to treatment or only after treatment, and thus, it was impossible to confirm any abnormalities noted.

Haematology was done in 85 patients only: 29 in each cetirizine group and 27 in the placebo group.

An increase in the white cell count was observed in - 8 patients from the 2.5 mg bd cetirizine group: before and after treatment in 3 cases, only prior to treatment in 3 other and only after treatment in the 2 remaining. In one case (patient no 204/004) the pre-treatment value (26.8 x 10⁹/l) returned to normal after treatment;

- 5 patients from the 5 mg bd cetirizine group: only prior to treatment in 1 patient, only after treatment in 4 patients.

In one case (patient no 142/011) the value observed after treatment was 26.2 x 10⁹/l, but no value had been obtained prior to starting treatment;

- and in 9 patients from the placebo group: before and after treatment in 2 patients, only prior to treatment in 5 patients and only after treatment in 2 patients.

With the exception of the 2 cases mentioned above (patients no 204/004 and 142/011), the abnormal values observed for the other patients were only slightly over the normal laboratory values. No signs of infection were noted prior to treatment nor were any noted during the course of the treatment. The abnormal values noted were probably fortuitous.

None of the changes noted in the other haematologic parameters were of any clinical significance, nor did they appear to be related to the treatment given.
The bilirubine was assessed in 40 patients only.
11 patients were in the 2.5 mg bd cetirizine group and, of these, the
bilirubine was estimated, in 5 cases, after treatment only;
18 patients were in the 5 mg bd cetirizine group and, of these, the
bilirubine was estimated in 4 cases prior to treatment only and in 3 after
treatment only;
11 patients were in the placebo group and, of these, the bilirubine was
estimated, in 1 case, prior to treatment only and, in 3 cases, after
treatment only. In one patient from the 5 mg bd cetirizine group (patient n°
999/002) the pretreatment value was very high but decreased after treatment
although it did not return to normal.

SGOT was assessed in:
- 26 patients from the 2.5 mg bd cetirizine group: it was only slightly
above the upper limit of normal in 1 case, both before and after treatment,
and, in another patient, after treatment only.
- 28 patients from the 5 mg bd cetirizine group: it was only slightly above
the upper limit of normal in 3 cases, prior to treatment only; in 1 case,
both before and after treatment; in 2 cases, after treatment only.
- 26 patients from the placebo group: it was only slightly above the upper
limit of normal in 1 case, prior to treatment only and in 1 case, both
before and after treatment. In 1 case, the level was found after treatment
two times higher than the upper limit of normal.

SGOT was assessed in 25 patients from the 2.5 mg bd cetirizine group and 26
patients from the 5 mg bd cetirizine group, no increase was observed; and in
25 patients from the placebo group: in 1 case, the level was found to be
20% greater than the upper limit of normal.

Cetirizine does not appear to influence hepatic parameters: slight
increased SGOT values were observed in 3 patients only; on the other hand, a
two times increased value was observed in 1 patient from the placebo group.

Urea was assessed in:
21 patients from the 2.5 mg bd cetirizine group
23 patients from the 5 mg bd cetirizine group
21 patients from the placebo group.
No change was observed under cetirizine.

Creatinine was assessed in:
26 patients from the 2.5 mg bd cetirizine group
27 patients from the 5 mg bd cetirizine group:
the level was found to be slightly above the upper limit of normal, for 1
patient, both prior to and after treatment.
26 patients from the placebo group.
Cetirizine does not appear to influence this parameter.
F. Patient compliance

- **Blood and urine levels** of the test compound:

  An urine sample had to be collected at each visit, and a sample of plasma retained at the final visit.

  Nevertheless, neither urine nor plasma was collected for 22 patients (v. App. IV)
  6 from the 2.5 mg bd cetirizine group
  8 from the 5 mg bd cetirizine group
  8 from the placebo group.

  The samples of the remaining 112 patients were analysed by the Dept. of Metabolism and Pharmacokinetics at UCB (7).
  Two abnormal results were found:
  two patients from the 5 mg bd cetirizine group (141/007 and 141/207),
  were found not to have cetirizine in either plasma or urine. The first of these patients returned five days after starting treatment because of an asthma attack. The second patient returned three days after inclusion in the study with urticaria.
  As these pharmacokinetics data only came to light after the clinical data had been subjected to analysis, both patients were included in the analysis of efficacy and thus influenced this group in a negative manner.
G. Calculation of plasma half-life

The plasma half-life time was calculated between 2 and 16 hours based on the normalised plasma concentrations obtained for 42 patients, 20 from the 2.5 mg bd cetirizine group and 22 from the 5 mg bd cetirizine group. The results indicate that the mean plasma half-life of cetirizine is between 5.2 and 7.2 hours.

H. ENT

Only 4 investigators carried out a detailed ENT examination for signs of perennial allergic rhinitis, both before and after treatment. The results are given in appendix VI and were so few as not to warrant inclusion in the analysis.
IV. DISCUSSION

According to the investigator, the 10 mg daily dose of cetirizine appeared to be most appropriate for the control of the symptoms of allergic rhinitis.

This was demonstrated by control of the symptoms of rhinorrhoea, pharyngeal drips and even nasal obstruction. The latter, which is reported to be relatively insensitive to antihistamines, was reduced by about 50% by this treatment (v. Table 7).

Sneezing, on the other hand, appears to be more amenable to the lowest dose which is the only dose significantly different to placebo. This could possibly be due to a statistical artefact as, in both active groups, the reduction in the severity of this symptom is approximately 70%, whereas it is only 52% on placebo.

As regards pharyngeal drips, the 5 mg bd cetirizine group does not differ from the placebo group. This brings the statistically significant difference (p = 0.03) which can be seen between the two cetirizine groups into question.

No statistically significant difference can be demonstrated between the three groups as regards the parameters for evaluation by the parents from Day 3 to Day 14, with the exception of "sore throat". Nevertheless, if the figures obtained on Day 1, prior to treatment, and then on Day 3, Day 7 and Day 14 are considered, it can be observed that it is mainly in the 5 mg bd cetirizine group that the evolution is most favourable and least in the placebo group (v. Table 8). In the same way, the maximum improvement registered among the three groups is found in the 5 mg bd cetirizine group, after 7 to 14 days of treatment (v. App. VII).

As regards tolerance, in some cases the relationship between the test product and the adverse event reported is doubtful, e.g. for tiredness reported on the third day of treatment only when on 5 mg bd of cetirizine, or diarrhoea which appeared on the twelfth day only in the 2.5 mg bd group, or abdominal pain on the fourth day in the latter group.
It would appear even more difficult to attribute a purulent rhinitis to the treatment given (placebo group) or severe pyrexia (2.5 mg bd cetirizine group).

On the other hand, tiredness and sleepiness as well as difficulty in waking, which all appeared after starting the treatment and disappeared two days later, or lasted for the duration of the study and disappeared upon completion of treatment, could be attributed to the test substance.
V. CONCLUSION

10 mg of cetirizine daily, given as 5 mg in the morning and 5 mg in the evening, has been shown to be active and well-tolerated in the treatment of perennial allergic rhinitis in children aged 6 to 12 years. Although no dose-related effect has been demonstrated, except in the relief of nasal obstruction, it would nevertheless appear that the dosage of preference is that of 10 mg/day (0.25 to 0.5 mg/kg/day). The best effect on all parameters, including global improvement but with the exception of pharyngeal drips, is produced at the 5 mg bd dosage. At this dose, the effect produced is more than satisfactory and the tolerance is excellent. Given the advantages of a single daily dose, it would be interesting to compare the daily dose of 10 mg, which has been shown to be effective and well-tolerated when given as 5 mg bd, to 10 mg given once a day.
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