CLINICAL REPORT CE90E022 - STUDY A043

DOUBLE BLIND STUDY OF CETERIZINE ON INDEPENDENT GROUPS
(single dose, every night, of 2.5, 5 or 10 mg depending on weight,
for 2 weeks) COMPARED WITH A PLACEBO GIVEN TO CHILDREN FROM 3 TO 16 YEARS
DEMONSTRATING ORL OR CUTANEOUS ALLERGIC PATHOLOGY
(Protocol PCE84L051)

INVESTIGATORS: Professor H.L. VIS
Dr. G. CASIMIR,
Paediatric Clinic
Hôpital Universitaire St. Pierre
Rue Haute 320
1000 BRUSSELS - Belgium

SUPERVISOR: C. ARENDT, UCB - Pharmaceutical Sector
Medical Research Clinic
Clinical Research and Development
Chemin du Foriest
1420 BRAINE-L'ALLEUD (Belgium)

02.05.1990
# TABLE OF CONTENTS

## SUMMARY

1.

## I. INTRODUCTION

2.

## II. MATERIALS AND METHODS

3.

## III. RESULTS

7.

5. Comparison with treatment followed previously 11.

## IV. DISCUSSION

12.

A. Nasal allergy 12.
B. Cutaneous allergy 13.
C. Dosage and dose 14.

## V. CONCLUSION

16.

## REFERENCES

17.

## TABLES:

19.

1. Characteristics of different groups of patients

20.

2. Distribution of weight

21.

3. Development of scores and comparison of groups (nasal pathology)

22.

4. Visual Analog Scale

23.

5. Global assessment of treatment (Frequency distribution - nasal pathology)

24.

6. Development of scores and comparison of groups (cutaneous pathology)

25.

7. Visual Analog Scale)

26.


27.

9. Comparison with previous treatment (nasal pathology)

28.

10. Comparison with previous treatment (cutaneous pathology)

29.

11. Results on basis of dosage (1 study - 24 patients)

30.

12. Results on basis of dosage (4 studies - 77 patients).
APPENDICES:

I. Nasal pathology
II. Cutaneous pathology
III. List of medicines taken before the study (nasal pathology)
IV. List of medicines taken during the study (nasal pathology)
V. List of medicines taken before the study (cutaneous pathology)
VI. List of medicines taken during the study (cutaneous pathology)
VII. Protocol PCF84L051
SUMMARY

Cetirizine was administered in variable doses depending on the weight (from 0.13 to 0.28 mg/kg/day) once a day for 2 weeks to children from 3 to 16 years suffering from nasal (perennial rhinitis) or cutaneous allergies (atopic dermatitis, urticaria).

Forty-eight patients were included in the study, with 24 in each of the two pathological groups, these being in turn sub-divided into two sub-groups of 12 patients who received either cetirizine or a placebo.

The assessment of the symptoms (nasal obstruction, rhinitis, conjunctivitis and sneezing for nasal pathology; pruritus, erythema, papules and oedema for the cutaneous pathology) was carried out by the investigator before and after 2 weeks of treatment using a 4-point scale (from 0 = symptom absent to 3 = severe symptom). The investigator also assessed the condition of the patient before and after treatment by means of a graduated Visual Analog Scale from 0 mm = very poor condition to 100 mm = excellent condition.

During the final visit, the investigator noted any undesirable side-effects that arose during the treatment and compared the results observed at the end of the study with those obtained previously with other treatments.

Finally, the investigator, patient and/or parents assessed the treatment globally, judging it excellent, good, average or bad.

Tolerance of the treatment was assessed on the basis of an anamnesis and a biological examination carried out before and at the end of treatment.

There was no difference between cetirizine and the placebo after 2 weeks of treatment. The two products produced comparable improvements in both pathologies.

The possible reasons for this failure are reviewed: the use of concomitant treatments, under-dosage of cetirizine, single daily dose, methodological error. Doses of from 0.1 to 0.3 mg/kg were well tolerated and did not produce any side effects.
I. INTRODUCTION

In animal and clinical pharmacology, cetirizine 2HCl has proved to be a powerful anti H1 with long-lasting action.

In adults, cetirizine has proved active in the treatment of rhinitis and urticaria, and this activity, classical for an antihistamine, only rarely produced a sedative effect (ref. 1 to 6).

The aim of this study was to confirm the effectiveness of cetirizine in paediatrics, in cutaneous allergenic ailments or in the ORL sphere, among children aged from 3 to 16.
II. MATERIALS AND METHODS

In a controlled double blind study, the activity of cetirizine was compared with that of a placebo in two independent groups of patients, these groups being in turn divided into two sub-groups depending on the pathology (nasal or cutaneous).

Forty-eight children had to be chosen who met the following criteria:

For inclusion in the study, the patients had to be aged between 3 and 16 years, and have a nasal or cutaneous ailment for at least 6 weeks, the allergenic origin of which had to be proven (RAST-cutaneous tests) and for the treatment of which, the use of an antihistamine was justified. The parents had to give verbal agreement.

The following could not be chosen for the study: children with urticaria sensitive to salicylic acids, or patients suffering from serious renal or hepatic insufficiency, Quincke's oedema, or undergoing an infectious episode, or those who were cortico-dependent or who could not be deprived, during the entire study, of the general and local administration of H₁ other than cetirizine (including ketotifen), cromoglicate, anticholinergics, β-sympathomimetics, corticosteroids or antibiotics.

Deprivation for 15 days had to be observed for ketotifen and corticosteroids; the other products had to be stopped at least 4 days before the beginning of the study. Prescription of one or other of these medicaments meant the automatic exclusion of the patient.

Cetirizine was given in the form of a concentrated solution of 10 mg/ml in a 25 ml drop-counting bottle, each drop containing 0.5 mg of cetirizine 2HCl (batch No. 99).

The placebo was in the form of a solution of identical appearance and taste, also in a drop-counting bottle (batch No. 98P).

The treatments were randomised taking account of the two types of allergic pathology. Patients with a nasal ailment were numbered 1 to 24 in the study, while those with a cutaneous ailment were numbered 25 to 48.
The products were to be administered once a day for two weeks, the dosage being adapted to the weight of the children.

The daily dose, administered every night, diluted in water, milk or orange juice, was fixed at:

- 5 drops, or 2.5 mg, for children weighing less than 25 kg
- 10 drops, or 5 mg, for children weighing from 25 to 50 kg
- 20 drops, or 10 mg, for children weighing more than 50 kg.

The treatment was assessed as follows: before treatment, then after two weeks of treatment, the investigator, using a 4-point scale: (0 = absent, 1 = light, 2 = moderate, 3 = severe) assessed the intensity of the following symptoms:
- for nasal pathology: nasal obstruction, rhinitis, conjunctivitis, sneezing
- for cutaneous pathology: pruritus, erythema, papules, oedema.

To evaluate the condition of the patient, the investigator also used a Visual Analog Scale from 0 mm = very poor condition to 100 mm = excellent condition.

During the final visit, the side effects had to be observed and a 4-point scale used (better - as good as - not as good as - as bad as) to compare the treatment with whichever treatment had been previously given. Finally, the patient and the investigator were asked to assess globally the value of the treatment, bearing in mind the therapeutic effect obtained and the undesirable effects observed; the treatment was considered excellent, good, average or bad.

A biologic examination was required at the time of selection of the patients, and was repeated at the end of the study. It consisted of measuring the following variables: red and white globules with blood group, sedimentation speed, haemoglobin, haematocrit, total bilirubin, triglycerides, urea, creatinine.
The following statistical methods were proposed:

a) Analysis of symptoms

To establish on the basis of symptoms, indication, visit and group:
- a statistical summary (actual numbers, average, standard deviation)
- a frequency distribution of scores, the results being analysed in terms of the development of the scores between Visit 1 and Visit 2 (improvement, status quo, deterioration).
- frequency distribution of the various negatives, zero and positives
- level of significance of this development (sign test for paired samples = p inter-group)
- a comparison of these developments between the 2 groups using A Fisher exact test on the proportions of improvements in the 2 groups (cetirizine versus placebo).

b) Analysis of the Visual Analog Scale

To establish on the basis of indication, visit and group:
- a statistical summary (actual numbers, average, standard deviation, minimum and maximum) in terms of differences between the 2 visits
- a t-test for paired samples (p inter-group) enabling the significance of the development to be tested (nullity of average difference)
- a comparison of these developments between the 2 groups by means of an analysis of the variance in the differences (p versus placebo).

A global analysis should also be carried out to study the factors, indications and treatments simultaneously.

c) Analysis of biological data

To establish a statistical summary on the basis of treatment and visit.

To compare before/after, for each treatment, by means of a t-test for paired samples followed by a calculation of the limits of inferior and superior confidence of the average difference.

For averages less than 10% (monocytes - basophils - eosinophils), to establish the comparison by using a t-test for samples paired with probability calculations based on the binomial distribution (p = 1/2, bilateral test).
d) **Analysis of global assessment**

To establish the frequency distribution of the results on the basis of indication and treatment, and the comparison of these distributions by means of a Fisher exact test after reassembling the excellent and good classes on the one hand, and the average and poor ones on the other, this comparison also having to be done with all the indications together.

e) All the tests are bilateral and the level of significance retained is 5%.
III. RESULTS

The study was carried out from 3rd December 1984 to 10th September 1986. It therefore lasted for 22 months instead of the 12 months envisaged in the protocol. The statistical analysis of the results was dealt with in a report CF87E142.

1. General information
   - Six patients were under 3 years of age
   - Two patients in the placebo group with "cutaneous allergy" took Lomudal during the study (patients Nos. 5 and 10)
   - In the "nasal allergy" group,
     five patients in the cetirizine group (patients Nos. 33, 38, 40, 41 and 42) and
     six patients in the placebo group (patients Nos. 26, 28, 34, 37, 39 and 43) took Lomudal during the study.
   - It should be noted that one patient (No. 32 with rhinitis and asthma) moved in the week before his inclusion in the study from a "dusty" house to a new house.
   - The period between the 2 visits, which was to be 14 days, was in fact 21 days in 20 cases.
The forty-eight patients all underwent the analysis of efficacy and tolerance:
- 24 in nasal pathology, of which:
  • 12 received cetirizine and
  • 12 received the placebo

- 24 in the cutaneous pathology, of which:
  • 12 received cetirizine and
  • 12 received placebo.
The diagnoses and the allergens in question are given for each patient in Appendices I (nasal pathology) and II (cutaneous pathology).

In the "nasal pathology" group, the 12 patients who had received cetirizine had rhinitis caused by an allergy to mites; 8 patients were also allergic to cat and/or dog hair; 2 patients were allergic to milk, 2 patients to wheat; 2 patients to pollen; 1 patient to egg white; 1 patient to penicillin.

In this group of perennial allergic rhinitis, 11 patients also suffered from asthma and 1 patient from repeated laryngitis.

Among the 12 patients who received the placebo, 1 patient was allergic to dog hair and pollen, while the other 11 patients were allergic to mites and cat and/or dog hair (5 patients), pollen (3 patients), egg white (1 patient), milk (1 patient).

11 patients also suffered from asthma and one of these also had atopic dermatitis. 1 patient had isolated perennial allergic rhinitis.

In the "cutaneous pathology" group, the 12 patients who received cetirizine had atopic dermatitis together with urticaria (2 patients), asthma (2 patients) and/or rhinitis (2 patients). 1 patient was allergic to milk, egg white and wheat, 10 others to mites and also to milk (4 patients), animal hair (2 patients), pollen (2 patients), wheat (1 patient). Cutaneous and RAST tests were negative for the 12th patient who had atopic dermatitis and major urticaria.

Of the 12 patients who received the placebo, 1 patient showed urticaria reactions to milk, the other 11 patients suffered from atopic dermatitis, either isolated (4 patients) or with asthma (7 patients) and/or rhinitis (3 patients). Out of these 11 patients, 9 were allergic to mites and 2 to milk; they were also sensitive to cat/dog hair (6 patients), pollen (2 patients), egg white (2 patients).
2. Demography

The patients, 17 girls and 31 boys, were aged between 9 months and 15 years, weighing from 8 to 62 kg and measuring from 73 to 174 cm in height (see Table 1). The weights were distributed as is shown in Table 2.

The comparison of the groups shows that all the parameters were comparable before treatment.

3. Efficacy

a) Nasal pathology

Table 3 shows the development in scores in the form of a statistical summary as well as the comparison of developments in the 2 treatment groups. The same assessment is carried out for the Visual Analog Scale (Table 4).

The development was favourable in the 2 groups and obtained statistical importance with regard to rhinitis (p = 0.016 in the two groups), nasal obstruction (p = 0.016 in the cetirizine group and 0.039 in the placebo group) and the Visual Analog Scale (p = 0.017 in the cetirizine group and 0.003 in the placebo group).

Cetirizine alone improves sneezing significantly (p = 0.008).

But the two products are never distinguished from one another in a statistically significant way.

The global assessment of the treatment by the investigator on the one hand and the parents or patient on the other is more or less comparable (Table 5). The treatment groups do not differ from one another here either:

cetirizine versus placebo p = 0.68 (opinion of the investigator) and p = 1.0 (opinion of the parents and/or patient) in the Fisher exact test.
b) Cutaneous pathology

Table 6 gives the development of scores in the form of statistical tables and Table 7 shows the comparison of developments in the two treatment groups.

It can be seen that cetirizine and the placebo both improved pruritus in a statistically significant way (p = respectively 0.039 and 0.008) and erythema (p = respectively 0.07 and 0.125), and do not differ from one another. Papules and oedema were not modified by the treatments. These two symptoms were not very marked before treatment.

The scores attributed to the Visual Analog Scale also increased in a statistically significant way in the 2 treatment groups (p=0.032 with cetirizine and 0.008 with placebo).

The global assessment of the treatment (Table 8) is comparable in both treatment groups whether carried out by the investigator or by the parents (or the patient) (p = 1.0 in the Fisher exact test in the two treatment groups).

4. Safety

Three side effects appeared during treatment with the placebo. In the three cases, there was an increase in appetite. No side effect appeared in treatment with cetirizine.

On careful study of the results of the biological examinations, certain anomalies were observed which seem to have no relation to taking the product:

- A statistically, but not clinically, significant increase in the percentage of basophils during treatment with the placebo (from 0.6% ± 0.9 before to 1.9% ± 1.9 after).

- A statistically significant increase in alkaline phosphatase (already high from the outset) was observed during treatment with cetirizine. It should be noted that even during the placebo treatment, the values exceed the upper limit (0-270 U.I.), and that this increase in phosphatase is of bone tissue origin (infant group).
Other anomalies were observed which do not have any connection with the taking of cetirizine either:

- increase in eosinophils (allergic origin)
- increase in triglycerides (patients not fasting).

It should be noted that the γ-GT of patient No. 12, which were abnormal from the outset (64 instead of 40 maximum) returned to normal after the treatment with cetirizine.

5. Comparison with treatment followed previously

The list of treatments with which the products being studied were compared on the basis of an anamnesis, and the results of the comparison are given in Tables 9 (nasal pathology) and 10 (cutaneous pathology).

a) Nasal pathology
Out of 14 comparisons, cetirizine was better 4 times, not as good 7 times and as bad 3 times. Out of 13 comparisons, the placebo was better 4 times, as good 3 times, not as good 4 times and as bad 3 times. None of the two products being studied seemed better than the products with which they were being compared.

b) Cutaneous pathology
Out of 16 comparisons, cetirizine was better 4 times, not as good 9 times and as bad 3 times. If the antihistamines only are considered, out of 13 comparisons, cetirizine was better 4 times, not as good 6 times and as bad 3 times.

Out of 14 comparisons, the placebo was better 5 times, as good 3 times, not as good 4 times and as bad twice.
IV. DISCUSSION

We will consider successively:
- nasal allergy
- cutaneous allergy
- dosage and doses.

A. Nasal allergy

Cetirizine significantly improves sneezing, rhinitis and nasal obstruction (conjunctivitis is more the reflection of an acute pathology, such as seasonal rhinitis, and was not very important from the outset).

The differences with the placebo are not significant.

Several remarks must be made:
1. all the patients also suffered from asthma and were treated for this ailment (theophylline and Lomudal®, see list of medicines taken before the study, Appendix III).

2. during the study, 5 patients out of the 12 in the cetirizine group and 7 out of the 12 in the placebo group were treated for their asthma (cf. list of medicines taken during the study, Appendix IV).

Lomudal® which, theoretically, was forbidden during the study was prescribed to 5 patients in the cetirizine group and to 6 patients in the placebo.

This would seem to indicate that:
a. the protocol was not properly adapted to the clinical reality of the experimentator, whose patients come to see him above all because of asthma (and, incidentally, rhinitis) rather than for an isolated perennial rhinitis, without asthma;

b. it is possible that Lomudal® had an effect on the rhinitis, masking the beneficial effect of the cetirizine when it is compared with the placebo.
B. Cutaneous allergy

While cetirizine significantly improves pruritus and more or less improves erythema, the placebo also acts well and significantly on pruritus, without, however, improving the other symptoms.

An examination of individual data shows that most of the patients suffered from eczema rather than urticaria (2 cases of urticaria in the cetirizine group and one case in the placebo group). Apart from pruritus and erythema, the symptoms which had to be assessed by the doctor (papules and oedema) were more typical of urticaria than of eczema.

This would explain why the symptoms, apart from pruritus and erythema were not very important at the outset and did not evolve much under treatment with cetirizine.

The action of the placebo on the pruritus is inexplicable, especially since no patient took any antihistamines DURING the study - or at least did not admit to taking any. In fact, we should not lose sight of the fact that before the study:

1. in the cetirizine group: 5 patients out of 12 had already used anti H<sub>1</sub> without any success, and 4 patients out of 12 had taken topical corticoids with successful results.

2. in the placebo group: 4 patients out of 12 had already taken antihistamines and 2 patients had taken corticoids without any success.

The list of medicines usually taken by the patient before the study is given in Appendix V, and that of the medicines taken during the study in Appendix VI (let us recall that anti H<sub>1</sub>, B<sub>2</sub>-mimetics, cromoglycate, and corticoids were forbidden during the study).

It is not impossible that the patients who did not improve with the treatments in the study returned spontaneously to their former treatments, unknown to the investigator.
C. Dosage and doses

Dosage of one dose per day was based on the plasmatic kinetics (t 1/2 9.30 h) and kinetic action (more than 50% of inhibition of the cutaneous histamine reaction 24 h after a single 10 mg dose - 0.15 mg/kg) measured in ADULTS.

A guideline study (ref. 7) shows that the urinary excretion kinetics of cetirizine in children is different from that of adults: in children from 10 to 12 years weighing 27 to 39 kg, the urinary semi-excretion time was 6.6 ± 0.7 h, whereas it was 9.7 ± 1.1 h in adults. This would be an argument in favour of 2 doses/day for children rather than only one.

However, a study recently completed (ref. 8) shows that in children from 6 to 12 years suffering from pollen rhinitis, there is no clinically pertinent difference between administering the cetirizine dosage (10 mg/kg/day) in a single dose or in two doses (5 mg x 2/day).

The doses of cetirizine administered in the study reported here ranged from 0.13 mg/kg to 0.28 mg/kg.

By studying the therapeutic result obtained from doses of cetirizine, it
Without being of significance, the comparisons nevertheless indicate that the best results are obtained with $\geq 0.20$ mg/kg/day. This fact seems to be confirmed by the results of the other two studies where the activity of cetirizine is distributed differently on either side of an average dose, i.e. 0.19 mg/kg/day (ref. 12) and 0.25 mg/kg/day (ref. 13).
No side effects were reported for any of these studies.

It would seem, therefore, that for most patients in this study, cetirizine was under-dosed. Doses higher than 0.20 mg/kg/day should be recommended for children, whether administered in a single daily dose or in two doses as suggested by the results of the pharmacokinetics.

All of these comments lose value, however, when the study is considered by itself. As already said above, the protocol does not seem to be adapted to the target group monitored by the investigator. In addition, the selection of patients called for by the protocol was not sufficiently clear for either of the pathologies. The fact that 2 types of pathology were chosen for the same study was also an error, worsened by the excessively low number of patients per group (4×12 patients). Moreover, the assessment was only made on two occasions, first of all before the study, and then after two weeks of treatment. No information was provided concerning the treatment period and particularly the deadline for the appearance of any improvements. A daily assessment card was not envisaged.

It should be noted that no checks were made to ensure the treatment was followed.

Under the conditions of the study, it was not very likely that any activity by cetirizine could be highlighted.
V. CONCLUSIONS

The effect of the cetirizine, administered to children aged between 3 and 16 years in doses varying from 0.1 to 0.3 mg/kg, taken once a day, with cutaneous (atopic dermatitis, urticaria) and nasal (perennial rhinitis) allergic pathologies, did not differ from that of the placebo.

The use of concomitant medication such as cromoglycate might have contributed to the effect of the placebo observed in the rhinitis.

The effect of the placebo in the pruritus is inexplicable except if one admits that certain topical medications had been administered unknown to the investigator.

A dose of at least 0.20 mg/kg/day should be recommended, taken once or twice daily.

Doses of 0.1 to 0.3 mg/kg were well tolerated and did not produce side effects.
REFERENCES

1. SABBAH A.
   Comparison of cetirizine and terfenadine in perennial allergic rhinitis.
   Alergología e Immunología Clinica
   1987 2/2 322 abstr. 431

2. KURZEA J A.
   Comparative study of cetirizine, terfenadine and placebo in the treatment of
   patients with perennial allergic rhinitis.
   Abstr. Symp. "Cetirizine, a new ERA in allergotherapy" Brussels (B)
   1987, March 27-30, 25

3. BERMAM B.
   Cetirizine therapy of perennial allergic rhinitis.
   1987 81/1 177, Abstr. 36

4. BROIDE D.H.
   Evaluation of cetirizine in the treatment of patients with seasonal allergic
   rhinitis.
   1988 81/1 176, Abstr. 31

5. BRUTTMAN G.
   Antiallergic effectiveness of cetirizine in patients suffering from hay-fever
   and asthma.
   Abstr. Symp. "Cetirizine, a new ERA in allergotherapy" Brussels (B)
   1987, March 27-30, 27

6. DOCKX P.
   Comparison of cetirizine and terfenadine in idiopathic urticaria.
   Abst. Symp. "Cetirizine, a new ERA in allergotherapy" Brussels (B)
   1987, March 27-30, 23

7. ucb P071. Urinary excretion after administration of a single oral dose to
   children.
   UCB internal report LE87B021 : E. BALTES.
8. Multicentre study of the efficacy and safety of cetirizine when given once or twice daily to children between the age of 6 and 12 years suffering from seasonal allergic rhinitis.
UCB internal report CE89A104 : Y. BAELEDE

9. BRUTTMAN G.
Etude de la cétirizine 2HCl dans le traitement de la maladie allergique à expression nasale chez l'enfant.
UCB internal report CF87A051

10. PEDRALI P.
Etude de la cétirizine 2HCl dans le traitement du prurit de l'eczéma chez l'enfant.
UCB internal report : CF87A071

11. PEDRALI P.
Etude de la cétirizine 2HCl dans le traitement de l'urticaire idiopathique chronique chez l'enfant.
UCB internal report : CF87A073

12. VAN NIEKERK Ch.
A double-blind parallel multisite study of the safety and efficacy of cetirizine compared to dextchlorpheniramine and placebo in the treatment of children with seasonal allergic rhinitis.
UCB internal report : CE87E152

13. WEINBERG E.
A double-blind parallel multisite study of the safety and efficacy of cetirizine compared to dextchlorpheniramine and placebo in the treatment of children with seasonal allergic rhinitis.
UCB internal report : CE87E151