STUDY OF THE DURATION OF ACTION OF CETIRIZINE
IN CHILDREN AGED 6-12 YEARS,
MEASURED WITH THE HISTAMINE SKIN TEST

(Protocol PCF88L021)

INVESTIGATOR: Dr. D. BARAN
Hôpital Erasme
route de Lennik 808
1070 Brussels

MEDICAL DIRECTOR: Dr. Y. BAELDE
UCB Pharmaceutical Division
Clinical Research and Development
Chemin du Foriest
B-1420 Braine-l’Alleud
Belgium

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SUMMARY

16 Children aged 6-12 years participated in a study aimed at determining the duration of action of a dose of 10 mg cetirizine. Histamine skin tests were used as the measurement instrument. These tests were performed before taking one tablet of 10 mg cetirizine, then 4, 8 and 24 hours after this dose. They were repeated 24, 48 and 72 hours after the 4th dose of 10 mg cetirizine administered at a rate of 1 tablet per day.

The result suggest that cetirizine inhibits the skin reaction to histamine by more than 95% with regard to papules and more than 85% with regard to erythema when measured 4 and 8 hours after a dose of 10 mg. This inhibition was still almost 74% (papule) and 70% (erythema) when measured after 24 hours, both following a single dose and after reaching a steady state.

Some inhibition of the histamine reaction was still noted 48 and 72 hours after the 4th cetirizine dose, but there were considerable individual variations.
I. **INTRODUCTION**

Cetirizine is a potent antihistamine which is effective and well tolerated by adults at a dosage of 10 mg/day as a single daily dose in the treatment of rhinitis and urticaria (1-6).

In children, a dosage of 10 mg administered in one or two daily doses has proved to be equally effective and well tolerated (7).

Pharmacokinetic studies have demonstrated that the plasma half-life of cetirizine is shorter in children (6h30) than in adults (9h30) (8). It is thus right to ask what the true duration of action of a single dose of 10 mg is in children.

We consider that the histamine skin test is most suitable for answering this question since it is known that the skin reaction is still inhibited in adults by more than 40% when measured 24 hours after a dose of 10 mg (9-10).

The purpose of the study reported here was therefore to determine the duration of action in the skin of a single daily dose of 10 mg cetirizine as measured by the degree of inhibition of the histamine-induced skin reaction 4, 8 and 24 hours after the administration of a single dose of 10 mg cetirizine and then 24, 48 and 72 hours after obtaining a steady state, i.e. after 4 days of treatment.
II. MATERIALS AND METHODS

The protocol was approved by the ethics committee of the Cavell Medical Institute in Brussels.

The children and their parents gave their written consent to participate in the study after having been given information of the nature of this study, its purpose, its duration and the procedure to be adopted, as well as possible drawbacks.

This was an open trial.

Sixteen institutionalized children, boys and girls aged 6-12 years, were required for this study. They had to present no known atopic condition and could be taking no medicines likely to affect the response to histamine, i.e. antihistamines other than the study product, a 2-week wash-out for these products had to be ensured (6 weeks for astemizole); also barbiturates, tranquillizers, antidepressants, neuroleptics, phenothiazines, corticoids (chronic use), immunodepressants, synthetic antimalarials; a minimum wash-out period of 4 weeks was required for all these products.

To be enrolled in the study, the patients had to show a significant response (papule of \( \geq 8 \) mm mean diameter*) in a histamine test performed before taking the first cetirizine tablet, and present no dermographism.

Children suffering from kidney, liver or heart failure were excluded from the study, as were those presenting haematological abnormalities, infections or conditions likely to be treated with one of the medicines listed above and which could interfere with the study results.

Children demonstrating hypersensitivity to hydroxyzine or cetirizine were also excluded.

Finally, it was ensured that each selected child was able to continue the study to its end.

Cetirizine was presented as tablets of 10 mg to be administered each morning on an empty stomach with 100 ml of water for 4 consecutive days, at the same time each day.

In order to ensure good compliance with treatment, cetirizine was administered under the supervision of a staff member at the institution where the child was a resident.

The study was performed over 7 days for each enrolled child.

*An amendment to the protocol was reported, having initially stipulated a minimum mean papule diameter of 10 mm.
A histamine skin test (refer to the description of the histamine test in Annexe I) was performed before taking the first tablet, then 4, 8 and 24 hours after this first dose. The child then received one cetirizine tablet each morning for the following 3 days. A histamine test was again performed 24, 48 and 72 hours after taking the 4th and last cetirizine tablet.

The action of cetirizine was evaluated by measuring the area of the papule and erythema 10 minutes after each provocation: the outlines of the papule and of the erythema initially drawn on the skin were noted on a transparent sheet for retention in the child's care record form.

The degree of inhibition encountered at the various times was expressed as a percentage relative to the reaction at time 0. The inhibition and its confidence interval were estimated each time after logarithmic transformation of the data.

Safety was evaluated from the complaints reported spontaneously by the patients and/or their guardians and recorded in the case record form.
III. **RESULTS**

The statistical analysis of the results has been reported (CE89C212).

A. **General information**

16 children were enrolled in the study between 02.02. and 02.03.1989. All complied with the inclusion criteria and were thus included in the analysis of efficacy and safety.

A statistical summary was prepared for the areas and percentage inhibitions. In order to normalize the distributions, logarithmic transformation was performed for estimating a 95% confidence interval for mean inhibition.

The inhibition and 95% confidence interval were calculated from the difference of the logarithms of area between each skin test and the baseline measurement (D1 + 0h). These results were retransformed for expression as % inhibition.

B. **Demographic data** (Table 1):

The 16 children enrolled in the study were 10 boys and 6 girls aged 6-12 years (mean ± SD = 9.7 ± 2), weighing 18-55 kg (mean ± SD = 35.1 ± 9.5) and 115-156 cm in height (mean ± SD = 139.1 ± 12.7).

The mean papule diameter at time 0 before treatment was 12.2 ± 2.8 mm (range: 8-17 mm).

C. **Efficacy**

The mean areas of the papules and erythema measured before taking the first cetirizine tablet and 4, 8 and 24 hours after this dose are shown in Table 2 (papules) and Table 3 (erythema). The percentage inhibition relative to time 0 is also reported in these tables.

In the 4th and 8th hours the papule was reduced by 95% and the erythema by 87%. The inhibition was still 70% and 55% respectively after 24 hours.

The data obtained 24, 48 and 72 hours after the 4th cetirizine dose, i.e. after achieving a steady state, are shown in Table 4 (papules) and Table 5 (erythema). The percentage inhibition relative to time 0 is also shown in these tables.

The areas of the papules and erythema 24 hours after medication were very similar following the 1st and 4th tablets.

Slight activity of cetirizine was still observed after 48 hours (<30% inhibition for the papule and <20% for the erythema); only the papule seemed to be still influenced by cetirizine after 72 hours (<30% inhibition relative to time 0).

D. **Safety**

No adverse effects were reported.
IV. DISCUSSION

The raw data for percentage inhibition reveal marked skew in the distribution of results at
With regard to the papules, the degree of inhibition exceeded 95% at times D1 + 4h and D1 + 8h. At times D1 + 24h and D4 + 24h the mean inhibition was about 74% and significantly greater than 40% (the lower confidence limits are 66% and 62%). Inhibition was still significant at times D4 + 48h (47%) and D4 + 72h (42%), but its estimation was less precise (between 18 and 65% and between 18 and 59%, respectively).

With regard to the erythema, the degree of inhibition exceeded 85% at times D1 + 4h and D1 + 8h. At times D1 + 24h and D4 + 24h the mean inhibition was about 70% and significantly greater than 40% (the lower confidence limits are 48% and 57%). Inhibition was still significant at times D4 + 48h (6-49%) but not at D4 + 72h (at 0%, the inhibition is within the 95% confidence interval).

In order to be able to conclude that a single dose of 10 mg cetirizine is active in children, an inhibition of at least 40% after 24 hours was set as the objective. Indeed, almost 70% inhibition was obtained 24 hours after a single or repeated dose.

However, it should be noted that major variability was observed with this method. After 24 hours the activity had disappeared in some patients, and the number of patients not protected against the histamine test increased to the 72nd hour. However, some patients were still protected after 48 hours (9 for papules and 6 for erythema) and 72 hours (8 for papules and 2 for erythema).
V. CONCLUSION

In this group of 16 children aged 6-12 years it was found that the skin reaction in the histamine test was still inhibited by about 70% when measured 24 hours after a dose of 10 mg cetirizine and irrespective of whether this was after a single dose or after reaching the steady state, i.e. after the administration of 10 mg/day for 4 consecutive days.

Some inhibition (27%) of the papule was still observed 48 and 72 hours after the 4th dose of 10 mg cetirizine, but the variability of the results does not allow definitive conclusions to be drawn.
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