STUDY A168

PHARMACOClinICAL REPORT RRCE92E2507

DOUBLE BLIND CROSS-OVER STUDY COMPARING THE EFFECTS OF TWO DOSE REGIMENS OF CETIRIZINE (1 tablet of 10 mg od and 1 tablet of 5 mg bid during 3 days) ON THE HISTAMINE-INDUCED WHEEL AND FLARE REACTION IN 6 TO 12 YEARS OLD CHILDREN.

(Protocol FC90B201)

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Final Version
20.08.92
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# Table of Contents

I. SUMMARY .................................................................................................................. 1.  
II. INTRODUCTION ......................................................................................................... 2.  
III. METHODS ................................................................................................................. 3.  
  1. Study design ........................................................................................................ 3.  
  2. Volunteers selection ............................................................................................ 3.  
  3. Test drugs and dosage ......................................................................................... 4.  
  4. Conduct of the study ............................................................................................ 5.  
  5. Efficacy variables .................................................................................................. 6.  
      5.1. Primary efficacy variables ......................................................................... 6.  
      5.2. Secondary efficacy variables ..................................................................... 6.  
  7. Statistical analysis .................................................................................................. 7.  
      7.2. Evaluation of the safety ............................................................................... 8.  
IV. RESULTS ..................................................................................................................... 9.  
  1. Demography ........................................................................................................... 9.  
      1.1. Number of subjects ...................................................................................... 9.  
      1.2. Eligibility ..................................................................................................... 9.  
      1.3. Missing histamine skin test data ................................................................ 10.  
      1.4. Duration of the study .................................................................................. 10.  
      1.5. Demographic details .................................................................................... 10.  
  2. Evaluation of efficacy ............................................................................................ 10.  
      2.2. Histamine skin test till 24 h after the first intake ......................................... 11.  
      2.3. Histamine skin test till 60 h after the last intake ........................................ 13.  
V. DISCUSSION ............................................................................................................... 16.  
VI. CONCLUSIONS ........................................................................................................ 18.  
REFERENCES ............................................................................................................... 19.  
TABLES I to XVI .......................................................................................................... 20 to 35.  
Figures 1 to 12 ........................................................................................................... 36 to 47.
I. **SUMMARY**

The effects of two dosages of cetirizine (1 tablet of 10 mg OD and 1 tablet of 5 mg BID during 3 days) were compared, by means of the histamine-induced wheal and erythema reaction in 6 to 12 years old normal children. Sixty-six volunteers were enrolled. Nine were withdrawn for personal reasons (3) or protocol violation (6) and 57 entered in the efficacy analysis, having received both regimens of treatment, in a double blind cross-over design. The analysed population had a mean (SD) age of 9.04 years (2.07) and consisted in 41 boys and 16 girls who were not allergic.

The 5 mg BID regimen had a higher and longer action than the 10 mg regimen. The geometric mean of the histamine-induced wheal surface area was 2 times smaller 24 hours after the beginning of the 5 mg BID regimen than after the beginning of the 10 mg OD regimen. Similarly the geometric mean of the histamine-induced wheal surface area was more than 5 times smaller 12 hours after stopping the 5 mg BID regimen than 12 hours after stopping the 10 mg OD regimen. The observed differences were statistically highly significant ($p < 0.001$) and pharmacologically relevant. The protection, expressed as median % inhibition of the wheal and erythema was significantly better ($p < 0.001$) with the BID regimen (88.61 % and 84.07 %) than with the OD regimen (47.76 % and 60.66 %).

During the 60 hours after the last tablet intake, BID regimen activity was still pharmacologically relevant up to 36 hours while, OD regimen activity was no more pharmacologically relevant at the same time (median inhibition at 36 hours: wheal = 21.82 % for BID versus 1.91 % for OD; erythema = 38.56 % for BID versus 17.85 % for OD).

Both treatment regimens were very well tolerated.

We can hypothesize that, in severe conditions (i.e. high pollen count or severe perennial exposure) treating with a BID regimen of cetirizine would have a better therapeutic effect than an OD regimen in children with allergic rhinitis.
II. INTRODUCTION

Cetirizine is a potent and selective anti $H_1$ drug, which is well-tolerated. In adults, the dosage of 10 mg OD is used for the treatment of either seasonal or perennial allergic rhinitis or of chronic idiopathic urticaria (1, 2, 3).

An open pharmacoclinical trial (4), performed in a group of 16 children of 6 to 12 years old, showed that, 4 and 8 hours after a single oral intake of 10 mg of cetirizine the histamine-induced skin reaction was reduced by more than 95% for the wheal and more than 85% for the erythema. Twenty hours later, that inhibition still reached 74% and 70% respectively for the wheal and erythema. These inhibitions were similar after single or repeated intake of cetirizine 10 mg tablet OD. Forty-eight and seventy-two hours after the 4th intake of cetirizine 10 mg tablet, the histamine-induced skin reactions were still somewhat inhibited but the individual variability was high. The plasmatic half-life of cetirizine is about 6 hours in 6 to 12 years-old children (5). Therefore, one could question if there is a difference between the pharmacological activity of an OD regimen of 10 mg tablet or a BID regimen of two 5 mg tablets.

The aim of this study was to compare the effect of cetirizine 10 mg once daily and cetirizine 5 mg twice daily on a histamine skin test. Originally it was intended to conduct the study on children aged between 6 and 12 years. In order to enroll a sufficient number of subjects within the time limits foreseen (end of the study in December 1991), it was decided on 8 November 1991 to broaden the age range to between 5.5 and 13 years.

The effect of cetirizine is measured by the inhibition of the development of wheals and erythema induced by a histamine skin test. In order to evaluate and compare the kinetics of the effect, the histamine skin test was performed four times in a period of 24 hours following the first intake, and five times at twelve hours intervals after the last intake, starting three days after intake of the medication.
III. METHODS

1. STUDY DESIGN

The design of the trial is that of a double blind, randomised, balanced, cross-over study on 60 institutionalised children.

The children were to receive 10 mg cetirizine during three consecutive days, either as 10 mg tablets to be administered in the morning and a placebo tablet to be administered in the evening (OD regimen) or as 5 mg tablets to be administered in the morning and in the evening (BID regimen). The two study regimens were followed in a double blind, cross-over, randomly allocated fashion, the two treatment periods being separated by a wash-out period of at least seven days. In each treatment period a baseline histamine skin test was performed before the first intake of the study medication. Consequently the histamine skin test was to be performed 4, 8, 12 and 24 hours after the first intake of study medication, and also 12, 24, 36, 48 and 60 hours after the last intake of study medication.
2. VOLUNTEERS SELECTION

To be eligible for the study, male or female institutionalized children ought to be aged between 5.5 and 13 years, without known atopic affection, not taking any medication susceptible of modifying the response to histamine, and developing, before the study, a wheal with an average diameter of at least 8 mm. Also, the child and its legal representative must be willing to give written informed consent.

Final Version
20.08.92
Excluded from the trial were children with atopy, renal, hepatic or cardiac insufficiency, hematological disease, infection, hypersensitivity to hydroxyzine or cetirizine, affections susceptible of being treated with a medication that might interfere with the results of the study; children having taken antihistamines in the two weeks preceding enrollment in the study or astemizole in the 6 weeks preceding enrollment, or having taken, in the month preceding enrollment, barbiturates, tranquillizers, antidepressants, neuroleptics, phenothiazine derivatives, corticoids in chronic usage, immunosuppressants, or synthetic antimaludan medication. Also excluded were children with dermographism, with an insufficient response to the baseline histamine skin test, those likely not to terminate the study, or having participated in another clinical trial during six months prior to preceding enrollment. Children for which any of these exclusion criteria occurred during the study were also to be excluded.

3. **TEST DRUGS AND DOSAGE**

Cetirizine : 10 mg tablets (batch 43)
5 mg tablets (batch 29)
Placebo : placebo tablets (batch 38P).
All tablets had an identical appearance.
4. CONDUCT OF THE STUDY

The study took place in two periods of six days, separated by a wash-out period of at least 7 days. During the week preceding enrollment in the study, the children were submitted to a general clinical examination, their medical history was recorded, and written informed consent was to be obtained. The results of a skin or prick test with Dermatophagoides extract, animal dander, grass-pollen and mixed weeds were to be available in order to exclude children with atopic affections. At least 10 minutes before intake of the first study medication in the first period, a blank skin test was to be performed simultaneously with a histamine skin test carried out on the other forearm, in order to eliminate children with demophobia or children with an insufficient response to the histamine skin test. The reaction to the histamine skin test should be characterized by a wheal with an average diameter of at least 8 mm. This average distance was defined as the average of the largest diameter of the wheal and the diameter orthogonal to the largest diameter.

During each treatment period histamine skin tests were performed at least 10 minutes before, and 4, 8, 12 hours after the intake of the first tablet, and five times after the intake of the sixth tablet, every twelve hours.
5. EFFICACY VARIABLES

5.1. Primary efficacy variables
The evaluation of the effects of the two treatment regimens of cetirizine on the histamine skin test were primarily based upon the surface of the wheals 24 hours after the intake of the first tablet and 12 hours after the intake of the last tablet of study medication (active or placebo). The evaluations were performed after logarithmic transformation.

5.2. Secondary efficacy variables
Secondary efficacy variables were the surface of the wheals 4, 8 and 12 hours after intake of the first tablet and 24, 36, 48 and 60 hours after the last intake of study medication, and the surface of the erythema during each of the histamine skin tests. All evaluations were performed after logarithmic transformation.

The evaluation of the effect of the two dosage regimens was also based upon the inhibition of the surface of the wheals and erythema expressed as a percentage of the baseline value. The percentage inhibition at a given time point t is calculated as:

\[ \text{% inhibition (t) = } \frac{\text{baseline surface} - \text{surface (t)}}{\text{baseline surface}} \times 100 \]

6. SAFETY VARIABLES

The evaluation of the safety is based upon the number of subjects spontaneously reporting adverse events during the study. The adverse events were classified according to COSTART terminology.
7. STATISTICAL ANALYSIS

(For details see Individual Data document RRCE92A2202 and Statistical Report Document RRCE92A2201).

All statistical tests were carried out two-sided at the 5% level of significance. Descriptive statistics were calculated for all variables recorded during the study. For discrete variables, descriptive statistics consisted of frequencies and percentages. For wheal and erythema surface areas, descriptive statistics were calculated after logarithmic transformation with base ten. Means were retransformed and the results are presented as geometric means of wheal and erythema surface area.

For the percentage inhibitions, means and standard deviation were calculated.

7.1. Evaluation of the efficacy

7.1.1. Wheal and erythema surface area

Analysis of wheal and erythema surface areas was carried out after logarithmic transformation with base ten. Comparison between OD and BID treatment regimens was performed according to the parametric method for cross-over studies described by Hills and Armitage (6).

The approach described by Hills and Armitage allows to investigate the effect of the treatment regimen (OD or BID), the effect of the period of administration (period I or II), and the interaction between these two factors. A significant interaction would indicate that a possible difference between the two treatment regimens is not the same in the two periods. If an interaction is present, one cannot pool the results of the two periods, and the treatment effect should be estimated only from period I, using techniques for independent measurements.
In the absence of a significant interaction effect, the significance of the period of administration indicates that there is a difference in response during the two periods. The significance of the treatment effect indicates a difference in response to the two study medications.

For the logarithmic transformed wheal and erythema surface areas 95% confidence intervals were calculated on the mean difference observed in the OD and in the BID regimen group. Anti-logarithmic transformation of the limits of these confidence intervals yields the limits of 95% confidence intervals on the ratio of the geometric means of the surfaces areas observed in the OD and the BID groups. In the absence of a significant treatment by period interaction the 95% confidence intervals are calculated after pooling the results of the two treatment periods, otherwise the 95% confidence intervals are calculated on the basis of the data of the first treatment period.

7.1.2. Percentage inhibition of wheals and erythema
Analysis of the percentage inhibition of wheals and erythema was carried out according to the non-parametric methods for cross-over studies (6).

7.2. Evaluation of safety
The frequency of subjects spontaneously reporting adverse events is compared in the two treatment groups using the McNemar test. The reported adverse events are evaluated in a descriptive way.
IV. RESULTS

1. DEMOGRAPHY

1.1. Number of subjects
group. Thus, 57 subjects, 29 in the OD/BID group and 28 in the BID/OD group were evaluable for efficacy. The reasons for exclusion of the subjects from the efficacy analysis are given in Table III.
1.2. Eligibility

For all 57 subjects considered in the efficacy analysis all inclusion and exclusion criteria were fulfilled. The blank skin test performed on the left arm, before any administration of study medication, indicated that none of the 57 subjects suffered from dermographism. For one subject, number 6 in the OD/BID group, the histamine skin test performed on the right arm before any administration of study medication, yielded a wheal with a mean diameter less than 8 mm (namely 6 mm). This subject was not excluded from the study, and terminated normally. She was therefore not excluded from the evaluation of the efficacy.
1.3. Missing histamine skin test data

For 9 of the subjects considered in the evaluation of the efficacy, histamine skin tests were not performed on all of the times foreseen. A summary of the missing data is given in Table IV. Thus, only 50 subjects, 25 in each sequence group, will be considered in the evaluation of the histamine skin test results 48 hours after the last intake of study medication. Only 48 subjects, 25 in the OD/BID sequence group and 23 in the BID/OD sequence group, will be considered in the evaluation of the histamine skin test results 60 hours after the last intake of study medication.
1.5. Demographic details
In the group of 57 children there were 41 males and 16 females, all caucasians. They had a mean (SD) age of 9.04 years (2.07), a mean (SD) height of 128 cm (11) and a mean (SD) weight of 27.8 kg (6.7) (see Table V). The documentation of allergy (skin tests or RAST) showed that the selected subjects were not allergic.

2. EVALUATION OF EFFICACY
and Armitage was used. No significant difference was found between the two regimen groups, between the two treatment periods, and there was no interaction between regimen and period. It can thus be accepted that the reaction to the baseline histamine skin test is comparable in the two regimen groups and in the two treatment periods, and that the wash-out period between the two periods was long enough.

2.2. Histamine skin test till 24 h after the first intake
For none of the variables, the interaction and the period effects are significant. The non-significance of the interaction between treatment and period indicates that a possible difference between the two treatment regimens is not significantly different in the two periods. The effect of treatment can therefore be evaluated on the basis of the data of the entire cross-over experiment. The non-significance of the period effect indicates that the wheal and erythema surface areas are not significantly different in the two periods.
For the wheal surface areas, a highly significant treatment effect is found 24 hours after the first intake of study medication which was the primary efficacy variable. On average a smaller surface area, e.g. higher percentage inhibition, is observed in the BID than in the OD group. No significant difference between treatment effects are found 4, 8 and 12 hours after the first intake of study medication, but for the logarithmic transformed data, the differences between the OD and BID treatment regimens after 8 and 12 hours are almost significant. For these evaluations there is a trend towards higher values of wheal surface areas in the BID groups (Table VIII; Figure 3).

Also for the erythema surface areas, a significant difference between treatment effects is found 24 hours after the first intake of study medication. On average, a smaller surface area is observed in the BID than in the OD group. A significant difference is also found 4 and 8 hours after the first intake of study medication, but the difference between OD and BID is then in the opposite direction as compared to 24 hours after the first intake. 4 and 8 hours after the first intake, on average a higher surface area, is observed in the BID than in the OD group. No significant treatment effect is found 12 hours after the first intake of study medication (Table IX; Figure 6).
A highly significant difference between treatment regimens is found 24 hours after the first intake of study medication for the % of inhibition as well as for wheal surface area; BID being superior to OD treatment regimen.
The % of inhibition of erythema are significantly or almost significantly higher for OD regimen than for BID regimen at times 4 and 8 hours after the first intake. Afterwards, the difference at time 12 hours is non significant but, at 24 hours, a highly significant better inhibition was found for the BID regimen.

2.3. Histamine skin tests up to 60 hours after the last intake of study medication

See Figures 7 to 12.
For the wheal surface area 12 hours after the last intake of study medication, a significant interaction is found between period and treatment. This indicates that, for this variable, the difference between the OD and BID treatment regimens is significantly different in the two periods. Since the results observed in the second treatment period might be influenced by the study medication taken during the first period, the estimation of the difference between the OD and BID regimens, should be based upon the results observed during the first treatment period.
For all other variables the interaction effect is not significant. The non-significance of the interaction between treatment and period indicates that a possible difference between the two regimens is not significantly different in the two periods. For these variables, the effect of treatment can therefore be evaluated on the basis of the data of the entire cross-over experiment.

For the wheals 36 hours after intake of the last study medication, a significant period effect is found. On average, a smaller wheal surface area is found in the first than in the second treatment period. For all other variables the period effect is not significant.

For the wheal surface areas, a significant treatment effect is found up to 36 hours after the last intake of study medication. On average, a smaller surface area is observed in the BID than in the OD group. The same observation can be made for the erythema surface areas until 48 hours after the last intake of study medication.

The percentage of inhibition up to 60 hours after the last intake are presented in Table XIII and Figures 9 and 12. The non-parametric statistical approach was used to evaluate the two treatment regimens.

Wheals were significantly (or almost) more inhibited after the BID regimen than after the OD regimen until time 36 hours. For the erythema the significantly better inhibition after BID regimen lasted until 36 hours as well.
3. EVALUATION OF SAFETY

All 66 children enrolled in the trial were considered for the evaluation of the safety since they all received study medication. The evaluation of safety is based upon the number of children reporting adverse events broken down by treatment regimen. For this description it was decided that if an adverse event occurred at any time after the onset of the first treatment period, but before the onset of the second treatment period, this adverse event is considered to occur during treatment with the regimen administered in the first period. This implies that in
On the 60 subjects who were evaluable for safety in both treatment periods, 5 subjects reported adverse events in both periods, 6 subjects reported adverse events only in the OD treatment period and 2 subjects only in the BID treatment period. The frequency of subjects reporting adverse events during the two treatments is not significantly different (McNemar test : p = 0.289).
All adverse events were considered to be not or improbably related to the study medication (Table XVI).
V. DISCUSSION

Considering that the plasmatic half life of cetirizine in 6 to 12 years old children is about 6 hours, a comparison of 2 regimens of administration was of interest. Ten mg administered once a day (OD), in the morning with a placebo in the evening during 3 days, was compared with 10 mg administered in two intakes (BID), 5 mg in the morning and in the evening during 3 days, in a double blind cross-over study in 57 normal children. The evaluation of the effects of the two regimens of cetirizine was primarily assessed on the histamine skin test 24 hours after the intake of the first tablet and 12 hours after the intake of the last tablet of study medication.

In baseline condition, before drug administration, the wheals and erythema were not statistically different from one period to the other (tables VI and VII). The sample size was calculated to detect such a difference that the ratio of the geometric means of the wheal area 24 hours after the first drug intake should be outside the range of 0.78 to 1.29. According to this calculation, 60 subjects were needed to reach that goal. Sixty-six subjects were enrolled and 57 subjects among them entered in the efficacy analysis.

24 hours after the first intake, the geometric mean of the wheal surface area was statistically different in the BID regimen compared to the OD regimen (BID: 12.53 mm² versus OD: 25.94 mm²; p < 0.001). The ratio OD/BID was 2.08 with a 95 % confidence interval ranging from 1.46 to 2.94, showing a lower limit higher than 1.29. Expressed as median % inhibition from the baseline, median inhibition after BID regimen was 83.52 % at time 24 hours compared to 49.25 % median inhibition for OD regimen, a difference which is highly statistically significant (p < 0.001) and pharmacologically relevant.

12 hours after the last intake, the geometric mean of the wheal surface area was statistically different in the BID regimen compared to the OD regimen (BID: 6.85 mm² versus OD: 38.55 mm²; p < 0.001).
The ratio OD/BID was 5.63 with a 95% confidence interval ranging from 3.62 to 8.76, showing a lower limit much higher than 1.29. Expressed as median % inhibition from the baseline, BID regimen resulted in 88.61% median inhibition after 12 hours compared to 47.76% median inhibition for OD regimen, a difference which is highly statistically significant (p < 0.001) and pharmacologically relevant.

Further evaluations of the kinetics of the effect of the two cetirizine regimens were done. The median % inhibition of the wheals were not significantly different after a 10 or a 5 mg tablet and reached a maximum of 95.24% and 94.77% median inhibition respectively after 4 hours. There was a significantly higher inhibition of the erythema 4 and 8 hours after a 10 mg tablet than after a 5 mg tablet but this difference is pharmacologically non relevant (4 hours: 90.09% versus 86.64% p = 0.007; 8 hours: 89.15% versus 84.90% p = 0.053). Thus, during the day after the first intake, at times 4, 8 and 12 hours, both regimens inhibited potently and similarly the histamine-induced wheal and erythema skin reactions.

During the 60 hours after the last tablet intake, BID regimen activity was still pharmacologically relevant up to 36 hours while, OD regimen activity was no more pharmacologically relevant at the same time. (Median inhibition at 36 hours: wheal = 21.82% for BID versus 1.91% for OD; erythema = 38.56% for BID versus 17.85% for OD). Thus, there are significantly higher inhibition of the wheal and flare for the BID regimen versus the OD regimen until 36 hours after the last intake of study medication.

Both regimens were very well tolerated by the children. All reported adverse events were considered to be not or improbably related to the study medication.
VI. CONCLUSIONS

In 6 to 12 years old normal children, a 5 mg cetirizine BID regimen resulted in a higher protection against the histamine skin test than a 10 mg cetirizine OD regimen. The observed differences were statistically significant and pharmacologically relevant showing that the geometric mean of the wheal area was more than 5 times smaller 12 hours after stopping the BID regimen than after stopping the OD regimen. The protection, expressed as median % inhibition of the wheal and erythema is significantly better with the BID regimen than with the OD regimen and lasted longer. These differences are pharmacologically relevant.

Therefore we can hypothesize that in severe conditions (i.e. high pollen count or severe perennial exposure) BID treatment regimen would have a better therapeutic effect than OD treatment regimen with cetirizine in children with seasonal or perennial allergic rhinitis.
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