STUDY A135 - CLINICAL REPORT RRCE91L1901

A DOUBLE-BLIND RANDOMIZED MULTICENTRE STUDY OF 3 PARALLEL GROUPS COMPARING THE EFFICACY AND SAFETY OF CETIRIZINE
(1/2, 1 or 1 1/2 10 mg tablets b.i.d. according to body weight), CROMOGLYCATE (20 mg inhalation capsules q.i.d.) AND PLACEBO IN THE TREATMENT OF PERENNIAL ALLERGIC ASTHMA IN CHILDREN AND ADOLESCENTS
(Translation from RRCF91G0101)

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SUMMARY

The efficacy of cetirizine (5, 10 or 15 mg 2x/day according to the body weight) was compared with that of cromoglycate and placebo in the treatment of mild perennial allergic asthma (grades 2 or 3 according to K. AAS) in children and adolescents.

Three hundred and forty-eight patients were included. After an observation period of 2 weeks during which only β₂-agonists by inhalation were permitted in case of asthma attacks, 117 patients received cetirizine, 114 patients received cromoglycate and 117 patients received placebo. The treatment was to be taken for 12 weeks. The FEV₁ and clinical symptoms were assessed regularly by the investigator (visits at 4-week intervals). The asthma symptoms and inhaled β₂-agonist consumption was noted daily by the patients.

- **Cetirizine** was different from placebo (and from cromoglycate) for the frequency of asthma crises and β₂ agonists consumption.
  
The improvements between the initial period and the total treatment period were as follows:

- **% days with asthma:**
  - cetirizine: from 47.3% to 31.0% (p = 0.039 as compared to placebo)
  - cromoglycate: from 38.6% to 31.7%
  - placebo: from 43.3% to 35.8%

- **% nights with asthma:**
  - cetirizine: from 25.5% to 16.7% (p = 0.009 as compared to placebo)
  - cromoglycate: from 19.2% to 17.4%
  - placebo: from 24.0% to 22.5%

- **% days and/or nights with asthma:**
  - cetirizine: from 53.0% to 34.9% (p = 0.006 as compared to placebo)
  - cromoglycate: from 44.4% to 35.0%
  - placebo: from 47.1% to 40.6%

- **% days with consumption of β₂-agonists or other anti-asthmatic drugs:**
  - cetirizine: from 48.2% to 31.2% (p = 0.006 as compared to placebo)
  - cromoglycate: from 39.8% to 35.1%
  - placebo: from 48.3% to 42.4%

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- **Cromoglycate** was not different from placebo. The compliance to the treatment (spinhaler) was lower in this group (79.7%) and the patients were less ill initially.

- Morning peak expiratory flow rates showed a more favorable evolution on ceterizine than on cromoglycate treatment (from 284.1 l/min to 297.0 l/min and from 295.3 l/min to 303.8 l/min, p = 0.0375) the differences with placebo (from 288.0 to 299.0) being not significant and the evening rates were better on ceterizine from 290.3 l/min to 306.7 l/min than on cromoglycate (from 305.1 l/min to 313.0 l/min p = 0.02) or placebo (from 299.8 l/min to 307.7 l/min p = 0.008).

- Ten patients from the ceterizine group (8.5%) left the study for inefficacy and/or adverse events, 17 from the cromoglycate group (14.9%) and 22 from the placebo group (18.8%) (p = 0.022 for the comparison ceterizine/placebo).

A stratified statistical analysis according to country (Sweden versus the other countries) was conducted in a second analysis. The results showed that:

- in Sweden:
  the incidence of daytime asthma and the initial $\beta_2$-agonists consumption was higher than in the other countries. The improvements seen on ceterizine and on cromoglycate treatment were not different from those observed on placebo.

- In the other countries:
  the improvement observed with ceterizine was greater than that seen in the cromoglycate group (lower room for improvement) or the placebo group, and the differences were statistically significant. (except for the peak expiratory flow rates).

Despite these marked differences between the countries, the interaction test treatment x country was not significant.

All 3 products were well tolerated. Gastrointestinal complaints were the most frequently reported symptoms in the ceterizine group; throat irritation was most frequently reported with cromoglycate. The incidence of somnolence was 1.7% in both ceterizine and cromoglycate group, and 0.8% in the placebo group.
I. INTRODUCTION

1. RATIONALE

Cetirizine is a powerful and selective antihistamine with a rapid and prolonged action (1, 2).

It is commercialized in all EEC countries for the treatment of allergic rhinitis and urticaria.

Clinical pharmacological studies of the skin and lung were conducted with cetirizine (using doses of between 10 and 30 mg per day). These showed:

- an inhibition of the eosinophils migration in the delayed hypersensitivity reaction induced by an antigen in the skin (3);
- an inhibition of bronchospasm induced by histamine (4);
- encouraging results in the model of bronchospasm induced by pneumoallergens (5).
- an inhibition of the eosinophils accumulation in the bronchial lavage 24h after an allergic bronchoprovocation (6).

Controlled clinical studies suggest that cetirizine could be effective in the treatment of perennial asthma treated with theophylline (7) or inhaled corticosteroids (doses of between 200 and 1000 µg/d (8)).

This clinical study was carried out to assess the effect of cetirizine in children with mild perennial asthma, by comparing it with cromoglycate and placebo.

2. OBJECTIVE OF THE STUDY

1. To compare the efficacy of cetirizine, cromoglycate and placebo, administered as prophylactic treatment to patients suffering from perennial atopic asthma (reduction of the asthma frequency, reduction of inhaled β2-agonists consumption)

2. To compare the safety of the 3 treatments: adverse events, laboratory tests.
II. METHODS

1. STUDY PLAN
   
   This was a double-blind multicenter study, each center randomizing its patients into 3 parallel groups: 1 cetirizine group (2 x 5, 2 x 10 or 2 x 15 mg/d according to body weight), 1 cromoglicate group, 1 placebo group).

   Twenty-eight centers participated in the study: 10 centers in Sweden, 7 centers in France, 6 centers in Belgium, 3 in Germany, 1 center in both Holland and Great Britain.
2. **SELECTION OF PATIENTS**

The patients included into the study had to be between 5 and 16 years old, weighing more than 15 kg, and suffering from a well documented atopic perennial asthma, either from the history (diagnosed for at least 6 months) or by at least one positive (skin or RAST) test for a perennial airborne allergen.

The severity of asthma had to correspond to categories 2 and 3 of the K. AAS scale (appendix 3, published in Allergy, **36**, 34-14, 1981).

FEV₁ had to be $\geq 80\%$ of the predicted value, or reversible to $\beta_2$-agonists (an increase of at least 20%) if it was between 50% and 80% of the predicted value.

The patients had to be treated with inhaled $\beta_2$-agonists (fixed dose or on demand) for at least 2 months.

All the patients (and their parents or guardian) had to give their consent for participation in the study.

**The following patients were not to be included into the study**

- Patients with asthma of categories 1, 4 and 5 according to the K. AAS scale.
- Pregnant women or women likely to become pregnant.
- Patients with history of status asthmaticus leading to hospitalization in the last 6 months.
- Corticosteroid-dependent patients or patients treated with inhaled corticosteroids at a dose greater than 200 μg/d.
- Patients with:
  - abnormal hematological or biochemical tests;
  - severe pulmonary infection;
  - infection of any system other than the ENT or upper respiratory tract;
  - active tuberculosis;
  - mucoviscidosis;
  - gastro-esophageal reflux;
  - difficulties with swallowing;
  - abnormal chest x-ray;
  - atopic dermatitis or severe allergic rhinitis not controlled by local treatment;
chronic urticaria or other dermatological disease, treated with antihistamines except if these treatments were stopped at the pre-selection visit (cf p 7. "wash-out periods");

- allergy to pollen except if the inclusion into the study is done at least 3 months before the pollen season;

- intolerance to cromoglycate or hydroxyzine;

- social, psychological or other risks of not complying with follow-up visits;

- an occupation or lifestyle where sedation possibly due to the cetirizine would represent a hazard.

3. TREATMENTS

3.1. Test products, dosage and dosage schedule

Cetirizine: breakable oblong tablets containing 10 mg - batch N°s: 44 and 52

Placebo of cetirizine: breakable oblong tablets of the same aspect. Batch N°: 45 P.

Cromoglycate: inhalation capsules containing 20 mg - batch N°: P 3013

3.4. **Concomitant treatments**

Only inhaled β₂-agonists were permitted, on demand in case of asthma.

In Sweden, and only in the event of an infection, theophylline was allowed for 2 consecutive days.
4. EVALUATION OF EFFICACY AND FREQUENCY OF MEASUREMENTS

4.1. Assessments made by the investigator at the visits

- **FEV₁**: expressed as a % of the predicted value

- **Specific physical examination**
  
  • **chest**:
    - cough, dyspnœa and wheezing, on a 4-point scale:
      0 = absent, 1 = mild, 2 = moderate, 3 = severe;
    - presence or absence of infection of the upper respiratory tract;
  
  • **skin**:
    - atop ic dermatitis and urticaria on a 4-point scale:
      0 = absent, 1 = mild, 2 = moderate, 3 = severe;

  • **E.N.T.**:
    - rhinitis and allergic conjunctivitis, also on a 4-point scale.
    - presence or absence of E.N.T. infection;

  • **reactivity to metacholine**: optional
    - measurement of the PC 20 at visits 2 and 5 (or the last visit in case of premature withdrawal from the study), if the respiratory condition of the patient allows.

  • **Evaluation of the activity of the treatment at the last visit**
    This evaluation was made for asthma, and possibly rhinitis, atop ic dermatitis and urticaria, on 5-point scales: excellent, good, moderate, poor, very poor.

4.2. Assessments made by the patients at the visits

- **Evaluation of the quality of life**, on visits 1 and 5 (or on the last visit in the event of premature withdrawal from the study).
  This evaluation was made using a non-graduated 100 mm visual analogical scale (see appendix 4).
4.3. Assessments made by the patient at home

Every day, the patients had to evaluate or measure:
- peak expiratory flow rate in the morning and the evening,
- diurnal and nocturnal asthma on two 4-point scales.*
- consumption of inhaled β₂-agonists (number of puffs)
- intake of any other drug.

All this information had to be carefully noted on the daily record cards which were given to the patients at each visit.
* Nocturnal asthma
  0 = no asthma, slept well
  1 = woke once because of asthma
  2 = woke several times because of asthma
  3 = did not sleep because of asthma

Diurnal asthma
  0 = no asthma
  1 = wheezing, occasional cough, some shortness of breath but not incapacitating
  2 = wheezing, shortness of breath, irritating cough, impairing the usual activities
  3 = severe asthma, unable to conduct usual activities
5. EVALUATION OF SAFETY

5.1. Adverse events or special events reported by the patients at the visits and/or on the daily record cards supplied to the patients.

All adverse events were described by the investigator regarding their incidence, severity, duration and relationship to the test drug.
5.3. **Laboratory tests**

Blood tests were performed at visit 1 and at the last visit:

- red blood cells
- hemoglobin
- hematocrit
- white blood cells + differential count
- total proteins
- SGPT/SGOT/gammaGT
- urea/creatinine
- total bilirubin
- triglycerides
- total IgE
8. STATISTICAL ANALYSIS

8.1. Analyses of efficacy:
Two "intention to treat" analyses of efficacy were conducted:

- a global analysis including all the treated patients, and covering the entire duration of the study.

- another stratified analysis by country (Sweden on the one hand versus all the other countries) including all the treated patients and for the whole duration of the study.

8.2. Daily record cards - calculation of the frequency and severity variables
Using the daily record cards, 5 derivative variables were calculated per period between the visits and for the whole length of the study.

A. Frequency of diurnal asthma
Number of days with asthma (i.e., number of days where the score of diurnal asthma is at least equal to 1) divided by the observation days.

B. Frequency of nocturnal asthma
Number of nights with asthma (i.e., number of nights where the total asthma score was equal to at least 1) divided by the observation days.

C. Frequency of diurnal or nocturnal asthma
Number of days with nocturnal or diurnal asthma divided by the number of observation days.

D. Frequency of β₂-agonists consumption
Number of days with β₂-agonists consumption (and/or other antiasthmatic drugs) divided by the number of observation days.

E. Severity index
According to the formula: \[ \{ (\text{ASD} + \text{ASN}) / 2 \} + \text{BET} \], where:
\text{ASD} = \text{mean diurnal asthma score of days with asthma}
\text{ASN} = \text{mean nocturnal asthma score of nights with asthma}
\text{BET} = \text{mean score of } \beta_2\text{-agonists consumption or consumption of other drugs calculated as:}
\begin{align*}
1 &= 1 \text{ puff/day} \\
2 &= \text{from 2 to 6 puffs/day} \\
3 &= > 6 \text{ puffs/day or other drug}
\end{align*}
The severity index is therefore scored between 2 and 6.
8.3. Statistical methods
   a. A descriptive statistical analysis of all the measured variables was performed.
   
   b. Global comparisons of the three groups and 2 by 2 comparisons using nonparametric methods for independent groups.
      - The Chi-Square and Exact Fisher Tests or the Cochran-Mantel-Hanzel test for dichotomic variables.
      - The Cochran-Mantel-Hanzel test for the frequency distributions of the scores.
      - The Kruskal-Wallis and Wilcoxon tests for the continuous variables.
   
   c. All the comparisons were made on the difference between the initial status (baseline) and the time considered.

Visits
At visits 3, 4 and 5, taking V2 as the baseline.

Daily record cards
For the periods (i.e. the intervals between 2 visits) 2, 3 and 4, taking period 1 as the baseline.
The overall period was also defined = the interval between visit 2 and the last evaluable day of the study.

d. When a patient left the study due to inefficacity or adverse events, his results at the time of withdrawal were used as an estimate for the missing values for the subsequent visits and periods (except for the total period).

e. Statistical significances:
   All the tests were two tailed and the significance levels were the following:
   $0.01 < p \leq 0.05 \quad = \quad \ast \quad = \text{significant}$
   $0.001 < p \leq 0.01 \quad = \quad \ast\ast \quad = \text{highly significant}$
   $p \leq 0.001 \quad = \quad \ast\ast\ast \quad = \text{very highly significant}$

8.4. Analysis of safety
Adverse events were notified and classified according to COSTART.

Assessment of the blood test results.
III. RESULTS OF THE GLOBAL ANALYSIS

Thirty-five centers intended to participate in the study; 7 withdrew because of insufficient recruitment. The list of investigators, with the number of patients included per center and per group in each country, is given in Appendix 1. The study was conducted in line with the Helsinki Declaration and after review by the relevant Ethics Committees (see Appendix 2).

1. TOTAL NUMBER OF PRESELECTED PATIENTS
   Three hundred and sixty-seven patients were preselected. Nineteen of them did not receive any treatment and were therefore not included in the analysis. The list of these patients is given in Appendix 5.

2. DEMOGRAPHY
   Three hundred and forty-eight patients (221 boys and 127 girls) aged between 5 and 16 years and weighing between 18 and 104 kg were selected and included in the study. A description of the patients is given in Table I. The groups were comparable from a demographic point of view and for the duration of asthma. There was a higher proportion of girls in the cromoglicate group (difference not significant).

3. COMPARISON OF THE BASELINES (Tables II and III)
   Although the differences were often minor, it is worth remarking that the patients in the cromoglicate group were systematically less severely affected than in the other two groups.
   The differences between cetirizine, cromoglicate and placebo are greatest for the frequency of diurnal asthma (47.3%, 38.6% and 43.3%) and the frequency of β₂-agonists consumption (48.2%, 39.8%, 48.3%). However, these differences were not statistically significant.
4. **PATIENT'S WITHDRAWALS** (Table IV)
   
   - Most of the patients remained in the study until its end:
     - 82.1% in the cetirizine group
     - 72.8% in the cromoglicate group
     - 69.2% in the placebo group
   
   - The percentage of patients who withdrew from the study for inefficacy or adverse events (= therapeutic failures):
     - 8.5% in the cetirizine group (10 patients)
     - 14.9% in the cromoglicate group (17 patients)
     - 18.8% in the placebo group (22 patients)
   
   Only the difference in the proportions of therapeutic failures between the cetirizine and the placebo groups is significant (p = 0.022).

   - 9.4% of patients from the cetirizine group, 12.3% of patients from the cromoglicate group and 12.0% of patients from the placebo group left the study for reasons other than the treatment (lost to follow-up, noncompliance with the protocol).

   - The details of the premature withdrawals and the reasons are given in Appendices 6 and 7.

5. **VARIABLES OF DAILY RECORD CARDS**

5.1. **Frequency of days with asthma** (Table V - Figure 1)

   Between the **first and the last period**: the frequency of diurnal asthma fell in all three groups - from 47.3% to 27.7% in the cetirizine group, 38.6% to 33.1% in the cromoglicate group and 43.3% to 33.3% in the placebo group.

   **For the whole treatment period** (= "total period"), the frequency was 31.0%, 31.7% and 35.8% respectively for the cetirizine, cromoglicate and placebo groups.

   Comparisons:
   - cetirizine - placebo : p = 0.039
   - cetirizine - DSCG : p = 0.066
   - DSCG - placebo : p = 0.798

   The details of the other comparisons, period by period, are given in Table V.

   The relative decrease (Baseline - Total period x 100) as compared to the baseline was 34% (34% less days with asthma) for cetirizine and 17% for cromoglicate and placebo.

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5.2. Frequency of nights with asthma (Table VI - Figure 2)
The frequency of nocturnal asthma between the first and the last periods fell from 25.5% to 14.0% under cetirizine, from 19.2% to 19.5% under cromoglycate and 24.03% to 22.5% under placebo.

For the whole treatment period (= "total period"), the frequency was 16.7%, 17.4% and 22.5% for the cetirizine, cromoglycate and placebo groups respectively.

Comparisons between the "total periods":
- cetirizine - placebo : p = 0.009
- cetirizine - DSCG : p = 0.006
- DSCG - placebo : p = 0.803

The details of the other comparisons are given in Table VI.

The relative decrease was 34% for cetirizine, 9% for cromoglycate and 6% for placebo.

5.3. Frequency of days and/or nights with asthma (Table VII - Figure 3)
Between the first and the last period, the frequency of diurnal asthma and/or nocturnal asthma fell in all 3 groups from 53% to 30.5% in the cetirizine group, 44.4% to 35.8% in the cromoglycate group and 47.1% to 38.4% in the placebo group.

For the whole treatment period (total period), the frequency was 34.9%, 35.0% and 40.6% respectively for the cetirizine, cromoglycate and placebo groups respectively.

Comparisons: cetirizine - placebo : p = 0.006
- cetirizine - DSCG : p = 0.149
- DSCG - placebo : p = 0.126

The other comparisons are given in Table VII.

The relative decrease was 34.1% for cetirizine, 21.4% for cromoglycate and 14% for placebo respectively.
5.4. **Frequency of β₂-agonists consumption or other anti-asthmatic drugs** (Table VIII – Figure 4).

In the calculation of the frequency of β₂-agonists consumption, the consumption of other anti-asthmatic drugs was also taken into account, they were considered as days with β₂-agonists consumption.

The frequency of days on which β₂-agonists were used fell in all three groups. They fell between the **first and the last periods**, from 48.2% to 31.0% on cetirizine, 39.8% to 36.1% on cromoglycate and 48.3% to 40.3% on placebo.

For **the whole treatment period**, the frequency was 31.2%, 35.1% and 42.4% for the cetirizine, cromoglycate and placebo, respectively.

Comparisons:  
- cetirizine - placebo : p = 0.001  
- cetirizine - DSCG : p = 0.015  
- DSCG - placebo : p = 0.314

The details of the other comparisons are given in Table VIII.

The relative decrease was 35% for cetirizine and 12% for cromoglycate and placebo.

5.5. **Mean severity index of the asthma** (Table IX)

The severity index of the asthma remained practically unchanged in all 3 groups.

Between the **first and the last periods** it changed from 2.73 to 2.69 on cetirizine, from 2.51 to 2.62 on cromoglycate and from 2.65 to 2.65 on placebo.

For **the whole treatment period**, the severity index was 2.69 for cetirizine, 2.72 for cromoglycate and 2.73 for placebo.

Comparisons:  
- cetirizine - placebo : p = 0.570  
- cetirizine - DSCG : p = 0.079  
- DSCG - placebo : p = 0.216

The details of the other comparisons are shown in Table IX.
5.6. **Mean score of diurnal asthma symptoms** (Table X)

The mean diurnal asthma symptom score (between 0 to 3) was already low initially and fell in all three groups between **the first and the last periods** (from 0.6 to 0.3 on cetirizine, from 0.5 to 0.4 on cromoglycate and from 0.6 to 0.4 on placebo).

For **the whole treatment period**, the mean score was 0.4 on cetirizine and cromoglycate and 0.5 on placebo. The comparisons cetirizine/cromoglycate and cetirizine/placebo were significant ($p = 0.022$ and $p = 0.023$).

The details of the other comparisons are shown in Table X.

5.7. **Mean score of nocturnal asthma symptoms** (Table XI)

The symptoms were even milder than those of diurnal asthma and remained practically unchanged between the first and the last periods (all the values oscillated between 0.2 and 0.3).

For the total treatment period, the comparisons cetirizine/cromoglycate and cetirizine/placebo were statistically significant ($p = 0.006$ and $p = 0.017$).

5.8. **Mean consumption of β₂-agonists** (Table XII)

The mean consumption (number of puffs/day) of β₂-agonists fell slightly between the **first and last periods** in all 3 groups and the fall was more marked on cetirizine: 1.47 to 0.97 for cetirizine, 1.30 to 1 for cromoglycate, 1.68 to 1.43 for placebo.

For **the whole treatment period**, the consumption was 0.89 for cetirizine, 1.12 for cromoglycate and 1.44 for placebo. The reduction was statistically significant for cetirizine as compared to placebo ($p = 0.012$).

**NB:** The other anti-asthmatic drugs were not taken into account in the calculation of β₂-agonists consumption.

The details of the other comparisons are shown in Table XII.

The relative decrease was 39% on cetirizine and 14% on cromoglycate and placebo.
5.9. **Morning peak expiratory flow rate** (table XIII - figure 5)

Between the **first and the last periods**, the morning peak expiratory flow rates (L/min) were improved in all three groups (from 281.4 to 302.0 for cetirizine, from 295.3 to 307.4 for cromoglycate and from 288.0 to 308.4 for placebo).

For the **whole treatment period** (= "total period"), the values were 297.0 on cetirizine, 303.8 on cromoglycate and 299.0 on placebo. The improvement was significantly better on cetirizine as compared to cromoglycate (p=0.037).

The details of the other comparisons, period by period are given in table XIII.

The relative increase was 5% on cetirizine, 3% on cromoglycate and 4% on placebo.

5.10 **Evening peak expiratory flow rate** (table XIV - figure 6).

The evening peak expiratory flow rate (L/min) improved **between the first and last period** in all three groups: from 290.3 to 310.6, from 305.1 to 315.7 and from 299.8 to 317.0 for cetirizine, cromoglycate and placebo.

For the **whole treatment period**, the values were equal to 306.7 on cetirizine, 313.0 on cromoglycate and 307.8 on placebo. The differences are significant between cetirizine/placebo and cetirizine/cromoglycate (placebo=0.008 and 0.020).

The details of the other comparisons are given in table XIV.

The relative increase was 6% on cetirizine, and 3% on both cromoglycate and placebo.
6. **ASSESSMENTS AT THE VISITS**

6.1. **The symptoms at the visits** (tables XV to XVII)

For all 5 visits and for the 3 symptoms (dyspnœa, wheezing, cough), the effect of cetirizine and cromoglycate seemed to be better than that of placebo.

**In summary, at visit 5 and as compared to visit 2, the results were as follows:**

- **Wheeze**: 19.8% improvement and 13.2% worsening on cetirizine, 11.8% improvements and 9.8% worsening on cromoglycate, 11.7% improvements and 15.3% worsening on placebo.
- **Dyspnœa**: 13.1% improvements and 9.4% worsening on cetirizine, 7.5% and 6.5% on cromoglycate, 5.8% and 10.7% on placebo.
- **Cough**: 18.7% improvements and 12.2% worsening on cetirizine, 17.6% and 13.7% on cromoglycate, 21.6% and 19.6% on placebo.

The differences at the visits between the three treatments were not significant for wheezing. Only the comparison cetirizine - placebo on visit 3 was statistically significant (p=0.038) for dyspnœa. Only the comparison cetirizine - placebo at visit 4 was statistically significant (p=0.030) for cough.

6.2. **FEV<sub>1</sub>** (table XVIII).

FEV<sub>1</sub> improved slightly on both the active products between the second and the last visit (from 88.7% to 92.5% on cetirizine, from 89.3% to 93.6% on cromoglycate). It fell slightly on placebo (from 89.5% to 87.8%).

These differences are statistically significant at all the visits and for all the comparisons between the two active products and placebo (p between 0.002 and 0.032). The details of the comparisons are shown in table XVIII.

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6.3. **Quality of life** (table XIX to XXIV).
Judging from the 6 questions put to the patients before and after treatment, quality of life improved slightly.

The differences between the three groups were not statistically significant, except for school attendance (cetirizine/placebo p = 0.029 cromoglycate/placebo p =0.015).

6.4. **Global evaluation of treatment** (tables XX to XXVI)
The frequency distributions of the scores can be summarized into "success" (i.e. excellent, good and average results) and "failures" (i.e. poor and very poor results).

For asthma they were:

- 88.2% success (11.8% failure) on cetirizine
- 78.6% success (21.4% failure) on cromoglycate
- 73.4% success (26.6% failure) on placebo

The comparisons between the three groups of the frequency distributions of the global evaluation (5 point scale) were not significant.

The results for rhinitis and urticaria or atopic dermatitis were too fragmentary. Therefore, only a descriptive analysis was made.

6.5. **Metacholine provocation test** (table XL)
Metacholine provocation tests were performed before and after treatment in 63 patients (results expressed in PD$_{20}$ for 6 patients and in PC$_{20}$ for 57 patients).
The results of PD$_{20}$ are given in table XL, but the small number of patients does not allow any interpretation of the results.
The evolution of PC$_{20}$ is also given in table XL.
The results show no modification of PC$_{20}$ before and after treatment in the 3 groups (ratio of the values at the last visit over the value before treatment : 1.0 in the cetirizine group, 1.5 in the cromoglycate group and 0.8 in the placebo group).
8. SAFETY

8.1. Adverse events (table XXVIII)

- The proportion of patients who reported adverse events (they were rather more side effects than adverse events) were similar in all three groups (23.9% with cetirizine, 24.6% with cromoglycate and 19.7% with placebo).

- Headache was the most frequently reported symptom in all three groups: (7.6% with cetirizine, 8.7% with cromoglycate and 11.9% with placebo).

- Gastro-intestinal complaints were most frequently seen with placebo (9.4%), followed by cetirizine (6%) and cromoglycate (2.6%).

- Irritating cough and irritation of the throat were most frequently seen with cromoglycate (6.1%), followed by placebo (1.7%) and by cetirizine (0.8%).

- Increase in body weight was most frequently seen with cetirizine (4.2%) and was similar in the other two groups (1.7%).

- The incidence of somnolence was low in all three groups (1.7% on cetirizine and cromoglycate and 0.8% on placebo).

There were no cardio-vascular or anticholinergic symptoms.
8.3. Assessment of the laboratory results

8.3.1. General evaluation
In all patients the two blood tests foreseen in the protocol were performed except for:
- 5 patients from the cetirizine group and 7 patients from the cromoglycate and placebo groups did not have the second series of tests (patients’ refusal).
- 1 patient from the placebo group refused the two controls (no. 336/4).
Overall, the changes observed at the end of the study as compared to the initial values were comparable in the three groups. Comparison tests did not show any statistically significant difference except for the SGOT where the threshold of significance is nearly reached (placebo=0.055), due to the fact that there were fewer abnormal increases in the SGOT (i.e. above the laboratory upper normal range) in the cromoglycate group (2/106 or 2%) than in the cetirizine group (6/110 or 6%) or the placebo group (9/107 or 8%).

8.3.2 Individual data
Careful review of the results of each patient, in particular for liver and renal test, showed a few abnormalities. The details of the lab test results which exceeded the norms by more than 10% are shown in table XXIX.
Eighteen patients from the cetirizine group, fifteen patients from the cromoglycate and nineteen patients from the placebo group fell into this category.
The higher values for the triglycerides were probably due to the fact that blood samples were not taken in the fasting state.
Only the increase in the transaminases of patient 315/014 (cetirizine group) was clinically relevant:
- The gamma GT results remained normal.
- The values returned to normal two months after the end of the treatment.
- The patient took ClamoxylR for a dental abscess between visits 4 and 5.
- Viral serology remained negative.
- Relationship to the treatment: possible.
IV. STRATIFIED ANALYSIS BETWEEN SWEDEN AND THE OTHER COUNTRIES

In addition to the global analysis, a statistical analysis not envisaged in the protocol was conducted, namely a stratified analysis between Sweden on the one hand (where more than one half of the patients were recruited) and all the other patients pooled together on the other hand. This, in order to study a possible country effect and the interaction treatment x country. The number of patients per country is insufficient to justify a stratified analysis by each country.

After comparing the baselines, only the frequency variables (symptoms of diurnal and nocturnal asthma, \( \beta_2 \)-agonists consumption), the peak expiratory flow rate and severity index were analysed, on the basis of the difference between period 1 (initial period) and the "total period" (whole treatment period).

1. COMPARISON OF THE BASELINES (tables XXX and XXXI)

Apart from sex and the frequency and score of nocturnal asthma, the Swedish patients were quite different from the others for the other factors: they were significantly older (and therefore larger, heavier with higher peak expiratory flow rates), the frequency and score of diurnal asthma were higher, as was the \( \beta_2 \)-agonists consumption. In contrast, the symptoms at the visits were less severe than in the other countries.
2. **STRATIFIED ANALYSIS**

2.1. **Frequency of diurnal asthma (table XXXII)**

In Sweden, the changes between the baseline period (period 1) and the whole treatment period (total period) for each treatment were as follows:

- **Cetirizine**: from 54.3% of days to 40.6% of days
- **Cromoglycate**: from 52.1% of days to 41.3% of days
- **Placebo**: from 56.1% of days to 42.3% of days

In the other countries, this change was from 41.5% of days to 23.2% of days for cetirizine, from 28.2% of days to 24.3% of days for cromoglycate and for placebo, from 34.3% to 31.3% of days. The treatment effect was significant ($p = 0.045$), but there was no country effect and the interaction treatment - country was not significant.

2.2. **Frequency of nocturnal asthma (table XXXIII)**

In Sweden, the evolution of the percentage of days with nocturnal asthma between period 1 and the total period was from 20.3% to 15.1% for cetirizine, and from 20.2% to 16.3% for cromoglycate, and from 23.1% to 19.6% for placebo.

For the other countries, the percentage changed from 29.6% to 18.0% for cetirizine, for 18.5% to 18.3% for cromoglycate, and from 24.7% to 24.6% for placebo. The treatment effect was significant ($p = 0.032$). There was no country effect and the interaction treatment - country was not significant.

2.3. **Frequency of diurnal and/or nocturnal asthma (table XXXIV)**

In Sweden, the evolution of the percentage of days between period 1 and the total period was from 57.3% to 43.5% with cetirizine, from 57.0% to 43.9% with cromoglycate, and from 59.7% to 47.2% with placebo.

For the other countries, the percentage changed from 49.4% to 27.9% for cetirizine, from 34.9% to 28.1% for cromoglycate and from 38.3% to 35.9% for placebo. The treatment effect was significant ($p = 0.018$), there was no country effect and the interaction treatment - country was close to statistical significance ($p = 0.065$).
2.4. **Frequency of β₂-agonists consumption (or other anti-asthmatic drugs)**  
(table XXXV)  
In Sweden, the evolution of the percentage of days between period 1 and the total period was from 56.2% to 42.9% for cetirizine, from 51.7% to 42.3% for cromoglycate, and from 57.8% to 48.2% for placebo.  
For the other countries, it changed from 41.7% to 21.6% for cetirizine, from 30.9% to 29.3% for cromoglycate and from 41.6% to 38.3% for placebo. The treatment effect was significant (p = 0.006). There was no country effect and the interaction treatment - country was not significant.

2.5. **Severity index (table XXXVI)**  
In Sweden, this index changed from 2.8 to 2.7 on cetirizine, from 2.7 to 2.8 on cromoglycate, and remained at 2.8 on placebo.  
For the other countries, it remained at 2.7 on cetirizine, it changed from 2.3 to 2.6 on cromoglycate and from 2.6 to 2.7 on placebo.  
Note that the minimum index is 2, and may increase up to 6 in severe asthma requiring more than 6 puffs of β₂-agonists per day or requiring the use of another anti-asthmatic drug.  
The treatment effect was not significant. There was no country effect and the interaction treatment - country was not significant.

2.6. **The morning peak expiratory flow rate (table XXXVII)**  
In Sweden, the morning peak expiratory flow rate changed from 324.3 to 334.7 on cetirizine, from 324.6 to 332.4 on cromoglycate, and from 331.4 to 341.4 on placebo. In the other countries it changed from 246.6 to 266.3 on cetirizine, from 272.8 to 281.6 on cromoglycate and from 256.9 to 269.0 on placebo.  
The treatment effect was not significant. There was no country effect and the interaction treatment - country was not significant.

2.7. **The evening peak expiratory flow rate (table XXXVIII)**  
In Sweden, the evening peak expiratory flow rate changed from 337.4 to 348.0 on cetirizine, 335.4 to 343.1 on cromoglycate, and from 347.5 to 351.7 on placebo. In the other countries it changed from 252.0 to 273.1 on cetirizine, from 281.2 to 289.2 on cromoglycate, and from 265.7 to 276.6 on placebo.  
The treatment effect was significant (p = 0.047), as was the country effect (p = 0.028). The interaction treatment - country was not significant.
V. SEPARATE ANALYSIS SWEDEN – OTHER COUNTRIES

Although the country effect was not significant (except for the evening peak expiratory flow rates) and no interaction was seen between treatment and country (except a trend for the frequency of diurnal and/or nocturnal asthma), one is impressed by the differences between Sweden and the other countries, and tempted to analyse the results separately.

The study was however not designed and not dimensioned for this kind of analysis.

Furthermore, increasing the number of statistical tests can lead to unwarranted conclusions.

The results given below should therefore be interpreted with great care and should be considered as a guide.

The mean values of the various data studied at period one and the final period are described in the previous chapter.
In summary

- **In Sweden**, the initial state of the patients is comparable in all three groups, and the improvement is very similar. The global comparisons as well as the 2 by 2 comparisons do not show any statistically significant difference except for the evening peak expiratory flow rate (comparison cetirizine - placebo : p = 0.035).

- **In the other countries**, the patients of the cetirizine group were more severely affected initially, followed by those of the placebo group, whereas the patients of the cromoglycate group were much less severely affected.

The therapeutic effect of cetirizine was markedly superior to that of placebo, which was itself very similar to that of cromoglycate.

The differences between cetirizine and placebo were statistically significant for the frequency of diurnal asthma, the frequency of nocturnal asthma, the frequency of diurnal and/or nocturnal asthma and the frequency of $\beta_2$-agonists consumption ($0.001 \leq \text{placebo} \leq 0.016$).

The differences were not statistically significant for the severity index and the morning or evening peak expiratory flow rates.

The differences observed between cetirizine and cromoglycate were statistically significant and in favor of cetirizine for the frequency of diurnal asthma, the frequency of nocturnal asthma, the frequency of diurnal and/or nocturnal asthma, the frequency of $\beta_2$-agonists consumption, the severity index, the evening peak expiratory flow rate ($0.004 \leq \text{placebo} \leq 0.038$ and close to the significance level for the morning expiratory flow rates (placebo $= 0.062$).

All the differences observed between cromoglycate and placebo were not significant.
VI. DISCUSSION

1. GLOBAL ANALYSIS

1.1. The initial condition of the patients (period 1 and visit 2)
The patients included into the study suffered from mild to moderate asthma corresponding entirely to the K.A.S criteria and were the kind of patients that were intended for the study (i.e. asthma with long symptom-free periods characterized by normal respiratory function and by the absence of β₂-agonists consumption).

Unfortunately, and despite the large number of patients, the patients in the cromoglycate group were less ill than the other patients. The differences were minor but consistent (both at visit 2 and during period 1) and not statistically significant.
It is nevertheless important to take this factor into account in the interpretation of the results because the potential for improvement was smaller in these patients from the beginning.

1.2. Efficacy of treatments
All the results are consistent and are to the advantage of cetirizine. The differences observed between cetirizine and placebo (and between cetirizine and cromoglycate) are nearly always statistically significant, even though the extent of the difference is sometimes small (these results are of the same order of size as those published for cromoglycate).

Cetirizine significantly reduced the frequency of asthma (-17.8%) and the frequency of β₂-agonists consumption (-16.6%) as compared to placebo (respectively -6.9% and -6.1%). In contrast, the severity of asthma, when it was present, remained unchanged (cf severity index). The reduction in the mean score of the attacks therefore results from a reduction in their frequency and not in their intesity (which was mild initially).

If the results are expressed in relative terms (to be able to compare them properly with the results of the literature) it can be said that the improvement of the symptoms (frequency and intensity) was about 34% with cetirizine, 21% with cromoglycate and 14% with placebo.
The benefit in the peak expiratory flow rate was small (less than 10% in all three groups) but was best in the cetirizine group.
Note that the room for improvement in respiratory function in the patients selected was small, as the FEV1 on inclusion was close to 90% of the predicted value.

The changes observed at the visits were only the reflection of the evolution of a condition characterised by long periods without any symptoms. These findings corroborated the data collected on the daily cards (better action of cetirizine, effect of cromoglycate comparable to placebo).

The results of this study are in line with those already published for cromoglycate.

In a study involving 397 patients with mild asthma, the relative improvement in symptoms on cromoglycate was 27% (13% on placebo) and there was an improvement in the morning and evening peak expiratory flow rate of 9% and 6% versus 6% and 1.2% on placebo (9). Another study using areosol cromoglycate (5 mg per dose/day) involving 139 patients showed very similar results (25% relative improvement in the symptoms versus 3.6% only on placebo, with slightly better results for the morning peak expiratory flow rate, which increased relatively by 14.7%, versus 4% on placebo) (10). If patients who respond to cromoglycate are preselected, the improvement is more marked (50% of reduction in symptoms versus 7.7% on placebo) (11).

The literature on ketotifen is more controversial. The improvements are only seen after the fourth month of treatment: improvement in the morning peak expiratory flow rate of 13.3% versus 7.7 on placebo after 22 weeks (12), reduction in concomitant drugs of 8.5% versus an increase of 43% on placebo after one year (13). Other studies have not shown any difference between the active product and the placebo (14) (15).
1.3. The problem of cromoglycate

The lack of activity of cromoglycate in this study is unexpected. Several hypotheses could explain this finding:
- the room for improvement was smaller in the cromoglycate group, the patients being less ill initially.
- the patient compliance with the capsules in the cromoglycate group (79.7\%) was not as good as for the tablets in the cetirizine group (99.0\%).

In order to verify this hypothesis, an additional analysis, not foreseen by the protocol was performed on the patients with a compliance for capsules $\geq$ 50 \% and for tablets $\geq$ 75 \%.
The results of the cromoglycate group are better than in the intention to treat analysis, but the comparisons with placebo (and cetirizine) are not significant.
The results of the cetirizine and placebo group are comparable to those of the intention to treat analysis, although some differences are no more statistically significant (smaller sample size).
Details of the results are given in appendix 8.
- there was a higher proportion of girls in the cromoglycate group than boys; asthma is thought to be more persistant in adolescent girls (16).

1.4. Safety

The incidence of side effects was comparable in all three groups (23.9\%, 24.6\%, 19.7\% for cetirizine, cromoglycate, and placebo respectively).

Sedation, particularly in the cetirizine group was less frequently reported in this study than in other clinical studies of asthma in adults.
2. Stratified Analysis by Country

The results observed in Sweden were different from those seen in the other countries. A few points are worth stressing. There is a surprising lack of correlation in Sweden between the number of symptoms observed at the visits (presence of asthma 20% of cases) and the frequency of symptoms reported on the daily cards (presence of attacks on 58% of the days).

Swedish patients are "educated" differently than in the other countries. There is a vast health program of sensitisation and prevention organized in specialized centers (strict monitoring with peak expiratory flow rates, eradication of house dust mites, sport. The consumption of inhaled β₂-agonists is much higher than in the other countries (58% of the days as compared to 38%), the patients use them more frequently and more rapidly — in some cases up to 14 puffs per day on average in this study. This high consumption can also explain the result of the placebo group seen in Sweden and mask the differences between the treatments.

Over-hasty conclusions must not be drawn from the results of the other countries. In fact, the study was not designed to make country by country comparisons. It is dangerous to multiply statistical tests and the differences between the groups before treatment are even more marked than in the global analysis.
VII. CONCLUSION

In this trial and all countries together, cetirizine (5 mg, 10 mg or 15 mg according to body weight) reduced the frequency of asthma. The frequency of β₂-agonist consumption is also reduced and the peak expiratory flow rates increased more in this group.

Stratified analysis by country clarified these results a little further.

In Sweden, the improvement was comparable in all three groups (marked placebo effect, patient education, higher consumption of β₂-mimetics). In the other countries cetirizine was markedly superior to the other treatment.

All three products were well tolerated clinically.

These results are encouraging but should be confirmed by further clinical studies in perennial asthma in children.
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