STUDY A106 - CLINICAL REPORT RRCE92K2901

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BRONCHIAL PROVOCATION TESTS WITH DERMATOPOHOIDIES IN SENSITIZED, SCHOOL-AGED CHILDREN: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE PROTECTOR EFFECT OF CETIRIZINE AND DETERMINATION OF THE OPTIMAL DOSE

(Protocol PCF87G251)

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TABLE OF CONTENTS

I. SUMMARY ............................................... 1

II. INTRODUCTION ......................................... 2

III. OBJECTIVES .......................................... 3

IV. MATERIALS AND METHODS .............................. 3
   1. ORGANIZATION OF THE STUDY ..................... 3
   2. SELECTION OF SUBJECTS ......................... 3
      2.1 Inclusion criteria ......................... 3
      2.2 Exclusion criteria ......................... 4
   3. DRUGS AND DOSAGES .............................. 5
      3.1 Test products ................................ 5
      3.2 Authorized concomitant therapies .......... 5
      3.3 Forbidden therapies ........................ 5
   4. STUDY PLAN ........................................ 6
   5. MEASURED VARIABLES .............................. 7
      5.1 Efficacy ....................................... 7
      5.2 Safety ......................................... 8
      5.3 Statistical analysis ....................... 9

V. RESULTS ................................................. 10
   1. DEMOGRAPHY ........................................ 10
   2. DESCRIPTION OF THE GROUP ...................... 10
   3. EFFICACY .......................................... 10
      3.1 Threshold of bronchial reactivity .......... 10
      3.2 Lung function tests ......................... 11
   4. SAFETY ............................................. 12
      4.1 Compliance .................................... 12
      4.2 Laboratory tests ............................ 12
      4.3 Adverse events .............................. 13

VI. DISCUSSION ........................................... 14

VII. CONCLUSION ......................................... 16

REFERENCES .............................................. 17

TABLES I to XI ........................................ 19-29

Final Version
10.02.92
I. SUMMARY

The effects of cetirizine (0.3 and 0.6 mg/kg per day for one week) and placebo on early allergic bronchospasm were measured in asthmatic children allergic to House Dust Mites in a double-blind, crossover study.

The threshold of bronchial reactivity to House Dust Mites and decreases in various lung function parameters were measured in bronchial provocation tests conducted after each treatment period. Twenty-seven (27) patients were included in the study. Six (6) were treated with 0.15 and 0.3 mg/kg cetirizine per day instead of 0.3 and 0.6 mg/kg/day.

The difficulties involved in conducting this study led us to explore the results rather than analysing them. This exploration suggests that the higher dose of cetirizine (0.6 mg/kg/day for one week) allows a clinically significant protection (reduction by half or more in allergic bronchospasm) as compared to placebo; each subject served as his or her own control.

The 3 doses of cetirizine and placebo were well tolerated.
II. INTRODUCTION

Specific allergen-induced bronchoprovocation in an atopic subject induces an early asthmatic response (EAR) within 5 to 10 minutes after the provocation which disappears spontaneously in the subsequent 1 or 2 hours. In almost half of the subjects, this early response is followed by a late response 4 to 12 hours after the allergen provocation (late asthmatic response = LAR).

The mast cells which contain histamine, play an important part in the early response (1). The late response is associated with the recruitment of neutrophils and eosinophils, which seem to play a pathogenic role, in the bronchial lumen (2) (3).

Both the older H₁ antihistamines (promethazine, chlorpheniramine, clemastine) and the newer H₁ antihistamines (terfenadine, azelastine, astemizole, cetirizine) produce a moderate inhibition of immediate allergen-induced bronchospasm in adults (4, 5, 6, 7, 8, 9).

Cetirizine is a potent and well-tolerated antihistamine. In the skin, cetirizine inhibits the immediate cutaneous reaction induced by an allergen, methacholine or compound 48/80 (10). It allows a significant dose-related protection against the bronchospasm induced by histamine in subjects with moderate asthma (11, 12). It also inhibits the migration of eosinophils in the late cutaneous response resulting from allergen provocation (13, 14).

Encouraging results have been obtained with cetirizine (10 mg, twice daily) in the preventive treatment of pollen-induced asthma (15). In one study, cetirizine treatment (10 mg, twice daily) protected patients with birch pollen-induced asthma (16). Finally, a double-blind, multicentre study conducted in France during the pollen season of 1988 showed cetirizine (15 mg, twice daily) to be significantly effective (17).

The aim of this study was to assess the effect of cetirizine on the immediate bronchospasm induced by an allergen provocation with a House Dust Mite extract in children allergic to house dust.
III. OBJECTIVES

The objectives of this study were to compare the protector effect of a chronic oral treatment with cetirizine at various doses versus placebo, and to determine the optimal dose, by conducting bronchial provocation tests with dermatophagoides allergen in sensitized, school-aged children.

IV. MATERIALS AND METHODS

1. ORGANIZATION OF THE STUDY

This was a double-blind, crossover study on a group of 27 patients with allergic asthma shown to be sensitive to Dermatophagoides pteronyssinus (DPT). The study compared 2 doses of cetirizine (0.3 mg/kg per day and 0.6 mg/kg per day in 2 divided doses administered over 1 week) versus placebo.

The study included a selection visit (V1), followed for each period by a beginning-of-period visit (V2, V4, V6). At each beginning-of-period visit, it was ensured that the patient was not receiving any other treatment, and the patient was given a supply of test treatment for the subsequent period. This was followed by an end-of-treatment-period visit (V3, V5, V7) at which the bronchial provocation tests with DPT were conducted. A final visit (V8) occurred 24 hours after V7. The protocol of the study was approved by the Ethics Committee of the Saint-Antoine University Hospital in Paris.

2. SELECTION OF SUBJECTS

2.1 Inclusion criteria

- Children of both sexes, between 6 and 12 years of age, weighing between 20 and 50 kg were included in the study. The written consent of a parent or legal guardian was required.

- Bronchial sensitivity to DPT was documented by:
  - a clinical history of atopic asthma,
  - a positive skin and/or RAST test for the allergen considered,
  - demonstrated pulmonary sensitization to the allergen considered,
  - reversibility of the bronchospasm by $\beta^2$-mimetics.
2.2 Exclusion criteria

- Acute bacterial or viral infection, intercurrent or recent (in the preceding 3 weeks), involving the ENT system or the upper or lower respiratory tract, and requiring specific and/or symptomatic treatment.

- Known allergy to hydroxyzine.

- Any chronic condition (renal, hepatic, cardiac...) which may interfere with the test treatment or evaluation of the response to treatment, or which requires chronic treatment with a drug other than cetirizine.

- Abnormally low body weight or obesity (defined as a difference of more than 15% above or below the ideal body weight for the height and sex of the subject).

- Malabsorption syndrome (Celiac disease, cystic fibrosis), symptomatic parasitosis.

- Clinically significant laboratory test abnormalities.

- Participation in another clinical study in the previous 3 months.

- Inability to understand or accept the objectives of the study.

- Inability to correctly use an aerosol inhaler.

- Previous use of:
  - oral or injectable corticosteroids (washout period: 8 weeks),
  - antibiotics (washout period: 3 weeks),
  - antihistamines (washout period: 1 week; for the special cases of ketotifen and astemizole, the washout periods were 2 and 4 weeks respectively),
  - disodium cromoglycate (washout period: 1 week),
  - oral β2-mimetics, inhaled corticosteroids and theophylline (washout period: 4 weeks).
3. DRUGS AND DOSAGES

3.1. Test products

The test drugs were allocated to the patients in an order determined by balanced random selection. The test drugs were presented in dropper bottles containing 100 ml of a drinkable solution containing 3 mg/ml (0.15 mg/drop, batch no 8115R-UCB batch 91) or 6 mg/ml (0.3 mg/drop, batch no 8114R-UCB batch 90) of cetirizine, or a placebo solution (batch no 8116R-UCB batch 92P) of identical taste and appearance.
3.2 Authorized concomitant therapies

An inhaled β₂-mimetic (fenoterol) was the only authorized concomitant drug, and was to be used only at the smallest dose necessary to control symptoms.

3.3 Forbidden therapies

Antihistamines other than the test product, locally acting or general vasoconstricting drugs, sedatives, and antiinflammatory drugs (in particular, aspirin) were forbidden during the study.
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Antihistamines other than the test product, locally acting or general vasoconstricting drugs, sedatives, and antiinflammatory drugs (in particular, aspirin) were forbidden during the study.
5. VARIABLES MEASURED

5.1 Efficacy:
Method of bronchial provocation

- The lung function parameters measured were:
  FEV1, MEF 25, MEF 75, MEF 25-75 and PEF.
5.2 Safety

All adverse effects were marked in the case report form, and, in the event of a serious or unusual problem, were reported immediately to UCB.

The investigator was responsible for the treatment of adverse effects. The patient was kept under observation until his or her condition returned completely to normal. Each patient was submitted to a battery of standard laboratory tests conducted and evaluated before the inclusion visit and on the last day of each treatment period (V3, V5, V7).

The following laboratory tests were conducted:

- Hematology: red blood cells, white blood cells with a differential count, hemoglobin, platelets, erythrocyte sedimentation rate, absolute eosinophil count
- Renal function: urea, creatinine
- Liver function: SGOT and SGPT, total and direct bilirubin, alkaline phosphatase, gamma-GT
- Urinalysis: pH, albumin, red blood cells, glucose, acetone, microscopy

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10.02.92
5.3 **Statistical analysis**

The protocol envisaged a comparison of the threshold concentrations at which the subjects responded to challenge with *Dermatophagoides* allergen after cetirizine (high dose), after cetirizine (low dose) and after placebo, using a variance analysis with a 3-treatment, 3-period crossover scheme by the method of Grizzle.

However, the difficulties encountered in conducting this study led us to abandon this analysis and attempt instead a more descriptive analysis (see Statistical Report RRCE91G0104 and Individual Data Document RRCE91C1101).

The envisaged criterion of evaluation was the threshold concentration of antigen which induced a bronchial reaction, as measured after each treatment period. This threshold was defined as the dose of allergen at which any of the lung function parameters measured dropped by 20% as compared to the initial value. In the experimental method used, these thresholds could be 1 IR, 2 IR or 4 IR.
V. RESULTS

1. DEMOGRAPHY

Twenty-seven (27) patients were included in the study. Six (6) patients (Nos. 2 to 7) received only half of the envisaged dose, in conflict with the protocol. Consequently, these patients received placebo and cetirizine at doses of 0.15 mg/kg/day and 0.3 mg/kg/day. Of the remaining 21 patients, 10 did not strictly follow the protocol, for reasons detailed in Table I.

The remaining 11 patients strictly followed the protocol.

2. DESCRIPTION OF THE GROUP

The group is described in Table II.

The 27 patients were 10 boys and 17 girls with a mean age (standard deviation) of 9.4 years (1.8 years), weighing 32.2 kg (7.8 kg) and measuring 136.1 cm (9.9 cm).

All patients had a positive skin test and a positive RAST to DPT. Twenty-five (25) of the 27 patients had a threshold of bronchial reactivity to DPT of 1 IR, 1 patient had a threshold of 2 IR, and for 1 patient the data were missing.

All the mean lung function parameters measured were higher than 70% of the predicted values.

3. EFFICACY

3.1 Threshold of bronchial reactivity

The protector effect of a drug can only be seen if the patient shows a stable threshold of reactivity on placebo, similar to the reactivity before treatment. Table III shows that 10 of the 19 patients had a threshold of bronchial reactivity on placebo similar to their reactivity before the study, demonstrating a reproducibility of the bronchial response induced by the allergen.

These 10 patients were used to study the possible protector effect of cetirizine (Table IV). Of these 10 patients, 6 were protected by one of the cetirizine treatments. However, there does not seem to have been a marked dose-effect response.
3.2 Lung function tests

To test the hypothesis under investigation, the results of the lung function tests were studied as follows:

All placebo patients who showed a drop, in the FEV, ≥ 15% or in the MEF 25, MEF 50 and MEF 25-75 ≥ 20%, were selected, and the dose of allergen at which this drop was recorded. Subsequently, the lung function values for the patient were checked at the same dose of allergen while he or she was receiving the different cetirizine treatments. The MEF 75 was not taken into account because too many data were missing. The PEF was not taken into account because this parameter is not very accurate.
4. **SAFETY**
4.3 Adverse events (Table XI)

Of all patients who received at least 1 treatment, 12 of the 23 patients under placebo, 1/6 under CTR 0.15, 12/25 under CTR 0.3 and 9/19 under CTR 0.6 reported adverse events.

The severity of the adverse events was not systematically noted, nor was the relationship to the test treatment. One (1) case of somnolence was noted under placebo and 2 cases of asthenia under CTR 0.3. Two (2) cases of nervousness were reported under placebo and 1 case under CTR 0.3.

The most frequently reported adverse events were those related to the allergy itself (asthma, cough, rhinitis).
VI. DISCUSSION

Because of the difficulties encountered in conducting this study in children with asthma due to house dust, there were numerous deviations from the protocol and patients did not go through all the envisaged bronchoprovocation tests.

For this reason, in agreement with the investigator, we have examined all the data from this study with the aim of arriving at some descriptive conclusions without undertaking a strict statistical analysis.

In total, 27 eligible patients entered the study. The threshold concentration which provoked a bronchial response was considered in the protocol to be the main parameter of evaluating efficacy. Of the 27 patients selected, 10 showed a stable response under placebo, implying that the threshold of bronchial reactivity was the same (1 IR or 2 IR) before treatment and under placebo (Tables III and IV).

In this group of 10 patients, apart from placebo, 1 patient received CTR 0.3 treatment only, 3 received CTR 0.15 and CTR 0.3, and 6 received CTR 0.3 and CTR 0.6.

None of the patients treated with CTR 0.15 (0/3) were protected, 4/10 were protected by CTR 0.3 and 2/6 were protected by CTR 0.6.

In all, 6 patients out of 10 saw an increase in their threshold of bronchial activity under treatment with 0.3 or 0.6 mg of cetirizine/kg/day. However, there seemed to be no obvious dose-effect response.

After considering these results, we examined the bronchoconstrictor response of each of the patients for each of the lung function parameters measured.

Considering all patients in the study, we looked for those who showed under placebo a bronchospasm characterized by a drop in the FEV, of at least 15% and/or a drop in the MEF 25, MEF 50 and/or MEF 25-75 of at least 20%.

The response of these patients under treatment with cetirizine at the same dose of allergen as placebo, is shown in Tables V, VI, VII and VIII and the results are expressed in terms of an absence (-) or presence (+) of a protector effect.

This protection can be considered to be clinically significant when the drop in the lung function parameter measured under cetirizine is less than half the drop seen in the same parameter under placebo, for the same dose of allergen.
Table IX shows that when all doses of cetirizine are considered, protection is seen in 70% of the cases on the FEV₁, 38% of the cases on the MEF 25, 44% of the cases on the MEF 50 and 38% of the cases on the MEF 25-75.

Table X confirms that the mean drops in these lung function parameters were smaller when the patients received cetirizine. A dose-effect response was seen in the patients who received CTR 0.3 and CTR 0.6 on the MEF 25, MEF 50 and MEF 25-75. For the FEV₁, even the CTR 0.3 dose produced a significant protection.

Two observations should be taken into consideration. First, Table X shows that whatever the lung function parameter measured, it was the dose of 0.6 mg/kg/day cetirizine that seemed to afford the best protection: a 1/3 reduction in the drop of the MEF 25 and a reduction of 3/4 in the drops of the FEV₁, MEF 50 and MEF 25-75. Note that the FEV₁ is considered to be a severe parameter in asthmatic children, and it is in this parameter that the frequency of protection was the highest (70%) (Table IX).

It is necessary to insist that these results are exploratory.

Under placebo, 12 patients out of 23 reported adverse events; 1/6 under CTR 0.15, 12/25 under CTR 0.3 and 9/19 under CTR 0.6.

One (1) case of somnolence was noted under placebo and 2 cases of asthenia under CTR 0.3. The most frequently reported adverse events were those related to the allergy itself (asthma, cough, rhinitis).
VII. CONCLUSION

The difficulties encountered in conducting this study led us to report the results descriptively rather than to analyse them statistically. This led us to conclude that the high dose of cetirizine (0.6 mg/kg/day for 1 week) seems to afford a clinically significant protection (reduction by half or more in bronchoconstriction) against the drop in the lung function parameters measured during a bronchoprovocation test with an inhaled allergen in asthmatic children. The various treatments were well tolerated clinically. The results of this study could be used to design a new protocol which would measure more accurately the protector effect of cetirizine, at a dose of 0.6 mg/kg/day, on the early phase of bronchospasm in asthmatic children allergic to house dust.
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