Title of Study: Characterization of Asymptomatic Methacholine Airway Hyperresponsiveness (MAHR) in Children: Budesonide or Placebo Turbuhaler® Treated.

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Study Code: 04-9203  CLINICAL STUDY SYNOPSIS
Report No.: 04-CR-9203


Study Period: September 1990 - February 1991

Clinical Phase: IV

Objectives: To determine the cellular profile of bronchial secretions collected by inducing sputum in children with asymptomatic MAHR as compared with secretions from normal children without MAHR and asthmatic children with a similar degree of MAHR.

To investigate whether the airway responsiveness to stimuli acting through indirect mechanisms (cold dry air) was better related to the presence of asthma symptoms than MAHR.

To compare the following parameters among the 3 groups: familial history of asthma and atopy; personal atopic status; rate of early life respiratory infections; presence, type and time since last respiratory infection.

To determine the effect of inhaled corticosteroid treatment on MAHR in the two hyperresponsive groups.

Study Design: This was a 2-part study. Study A was a 2-week cross-sectional observational survey of 3 groups: NC, no past or current history of asthma and without MAHR; AC, no asthma symptoms with MAHR; SC, asthmatics with a similar degree of MAHR to AC. Study B was a randomized double-blind 2-week cross-over trial (with a 2-week wash-out period) of the effect of budesonide versus placebo treatment on MAHR in groups AC and SC.
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Number of Patients: 41 subjects/patients in Study A, 20 males and 21 females. 28 hyperresponsive patients in Study B, 15 males, 13 females. Groups NC and AC had 13 members; group SC, 15.

Diagnosis and Criteria for Inclusion: Male and female non-smoking children aged 9-15 years were eligible (actual age range was 11-16 years). Group NC members were asymptomatic and had PC_{20} > 16mg/ml. Group AC members were asymptomatic, with MAHR defined as PC_{20} < 8mg/ml. Group SC members were asthmatics i.e. current symptoms for the last 2 weeks controlled only by inhaled β_{2}-agonists on demand, with MAHR, PC_{20} < 8mg/ml.

General inclusion: children had to be able to perform reproducible maximum expiratory flow manoeuvres with a coefficient of variation of <5% for FEV\textsubscript{1}; able to demonstrate FEV\textsubscript{1}/VC > 75% and FEV\textsubscript{1} > 70% of predicted normal at baseline; informed consent; no evidence of other respiratory disease such as cystic fibrosis, chronic bronchitis with sputum production or chronic cough (past or present); no exposure to allergens to which they were sensitive (with the exception of house dust mite) within 1 month of study start; no known allergy or irritability to inhaled budesonide; no alcohol or drug abuse problems; no use of oral or inhaled steroid, sodium cromoglycate or antibiotics within 1 month of study start.

Investigational Product: Pulmicort® (budesonide) Turbuhaler®, AB Astra 200μg/actuation, 200 doses, Lot # PK36, Exp. 11/91

Reference Therapy: Placebo Turbuhaler®, AB Astra; 0μg/actuation; Lot # PG 28, Exp n/a

Duration of Treatment: 2 weeks ± 3 days
Assessment Methods:
Study A (4 visits): Asthma questionnaire #1 (medical and familial asthma and allergy history); allergy skin tests; spirometry (FEV₁, VC, FEV₁/VC); methacholine challenge (PC₂₀), cold dry air challenge (PD₁₀); spirometry following sputum induction with hypertonic saline; analysis of sputum quality; determination of total cells, eosinophils, metachromatic cells in sputum; analysis of total cells, basophils, eosinophils and IgE in blood.

Study B (4 visits): Asthma questionnaires #2 and #3, covering severity of asthma symptoms and change in asthma or breathlessness after treatment; spirometry; methacholine challenge.

Statistical Methods:
In all tests of significance, 2-tailed alternatives were used and p < 0.05 was considered statistically significant. Relationships between arithmetic data were analyzed using the Spearman rank correlation coefficient.

Study A: Comparisons between groups were done with the χ² test and Fisher's exact test for 2-category data, and the Kruskal-Wallis test for greater than 2-category and arithmetic data. ANOVA tests on ranked scores were used to contrast between 2 groups if p < 0.1.
Reproducibility of scores and cell counts was assessed by calculation of the coefficient of repeatability derived from an ANOVA on repeated measures.

Study B: Treatment effect was assessed using ANOVA test for each group on changes from baseline to the end of treatment for log PC₂₀, FEV₁, VC and FEV₁/VC expressed as %PN. Effects of carry-over, treatment, period and sequence were considered.

Summary of Results:
Study A: the cross-sectional survey showed that the various physiological parameters examined exhibited a pattern for group AC distinct from both the NC and SC groups. This was particularly true for the cold air challenge in
which statistically different PD_{10} values were recorded between all 3 groups i.e. 0/13 NC, 4/13 AC and 11/15 SC children responded to cold air. Spirometric indices were generally 100% PN (or better) for all groups, although a statistically significant difference in VC%PN was recorded between the AC and SC groups. Chest tightness after methacholine challenge was increased to the same degree in AC and SC children, compared with the NC group. A similar trend was recorded for atopy, serum IgE, total white cell and basophil cell counts in blood. In contrast, group AC had numbers of blood monocytes closer to those found for the NC group and the SC group. Numbers of blood eosinophils, neutrophils and lymphocytes were comparable in all 3 groups. No significant differences in induced sputum sample quality or total white cell counts in sputum were found among groups. However, group SC had highly elevated eosinophil and metachromatic cell counts in sputum, while the AC group was not different from the NC group. Other than MAHR, no common factor was consistently recorded for all members of group AC.

Study B: the results of the cross-over trial showed that there was no apparent effect of budesonide on group AC, as judged by symptom scores and FEV_{1}%PN, in contrast to the statistically significant effect experienced by group SC. Variability in asthma state was recorded for group SC but not AC. Higher PC_{20} values were recorded in group SC only after budesonide treatment, whereas 2-fold and 4-fold increases in PC_{20} (after placebo and budesonide, respectively) were recorded for group AC.
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Conclusions: This study provided no evidence for an association of MAHR in asymptomatic children with the presence of ongoing inflammation in the airway. Some aspects of mild asthma were recorded for some asymptomatic children with MAHR, but no definitive sub-population could be identified. Inhaled budesonide was effective in improving symptoms and PC_{20} values in asthmatic children, but had no statistically significant effect on asymptomatic children with a similar degree of MAHR.

Date: 9/11/95

Signatures:

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