Sensitisation to Airborne Moulds and Severity of Asthma: Cross-Sectional Study from the European Community Respiratory Health Survey


Purpose of the Study. To assess whether the severity of asthma is associated with sensitization to airborne moulds rather than to other seasonal or perennial allergens.

Study Population. One thousand one hundred thirty-two adults 20 to 44 years old with current asthma and with skin prick test results.

Methods. Participating centers of the European Community Respiratory Health Survey of over 30 centers (13 countries) randomly selected samples of 20- to 44-year-olds. They completed a short postal questionnaire about asthma symptoms. Twenty percent of random subsamples from this group were invited to come to a test center for skin prick and blood tests, spirometry, and methacholine challenge. Severity of asthma was determined according to the frequency of sensitization to moulds (Alternaria alternata or Cladosporium berarum, or both) increased significantly with increasing asthma severity (odds ratio: 2.34; 95% confidence interval: 1.56–3.52) for either severe or mild asthma). This association existed in all of the study areas (gathered into regions), although there were differences in the frequency of sensitization. There was no association between asthma severity and sensitization to pollens or cats. Sensitization to Dermatophagoides pteronyssinus was also positively associated with severity. In multivariable logistic regressions including sensitization to moulds, pollens, D. pteronyssinus, and cats simultaneously, the odds ratios for sensitization to moulds were 1.48 (0.97 or 2.25) for moderate mild asthma and 2.16 (1.37–3.35) for severe mild asthma (P < .001).

Conclusions. Sensitization to moulds is a powerful risk factor for severe asthma in adults. This should be taken into account in primary prevention, management, and patients' education.

Reviewer's Comments. This is an interesting study of adults living in multiple countries and environments showing that sensitization to Alternaria and Cladosporium were actually associated with more severe asthma while sensitization to pollens and pets were not. Dust mite sensitization was also associated with more severe asthma as has been observed in previous studies. Previous studies have shown that exposure and sensitization to moulds is associated with death from asthma and life-threatening exacerbations. However, this is the first population-based study that used criteria other than just health care attendance alone, and included spirometry, steroid use, and frequency of asthma attacks. It is also interesting to see that mould was important in various areas of the world and different environments.

Wanda Phipatanakul, MD
Boston, MA

β-Adrenergic Agonist Therapy

Low-Dose Levalbuterol in Children with Asthma: Safety and Efficacy in Comparison with Placebo and Racemic Albuterol


Purpose of the Study. Racemic albuterol (RAC) consists of equal parts of (R-) and (S)-albuterol, with all the therapeutic activity being found in levobutlerol (LEV), the (R)-isomer. In addition to lacking bronchodilating activity, (S)-albuterol might have properties, suggested by in vitro studies, that might exacerbate airway reactivity and impair asthma control. The authors sought to determine if LEV results in improved safety and efficacy in children.

Study Population. Children 4 to 11 years old with asthma severity ranging from mild intermittent to moderate persistent were included if baseline forced expiratory volume in 1 second (FEV₁) was between 40% and 85% of predicted with at least 15% reversibility to RAC at screening.

Methods. Children in this multicenter, randomized, double-blind study received 21 days of LEV (0.31 or 0.63 mg), RAC (1.25 or 2.5 mg), or placebo 3 times daily. Ventolin (GlaxoSmithKline, Research Triangle Park, NC) metered-dose inhalers (MDI) and Nebules (GlaxoSmithKline, Research Triangle Park, NC) were available as rescue medications. The primary endpoint was peak percent change in FEV₁ after receiving study medication on day 21. Diary cards were kept, and the Pediatric Asthma Caregiver's Quality of Life (QOL) Questionnaire was administered at
days 0 and 21. Adverse events (AEs), serum potassium and glucose, vital signs, and electrocardiograms were monitored.

Results. All 4 active treatments significantly improved the primary endpoint versus placebo (P < .001), with FEV₁ immediately after nebulization as follows: placebo, 2.0%; LEV 0.31 mg, 19%; LEV 0.63 mg, 18.1%; RAC 1.25 mg, 12.4%; and RAC 2.5 mg, 15.6%. Both LEV doses led to significantly greater improvement in FEV₁ versus RAC 1.25 mg (P < .05). LEV 0.31 mg was the only treatment not significantly different from placebo for changes in heart rate, QTc interval, and glucose. All active treatments decreased serum potassium. There was no evidence of desensitization to either LEV or RAC as measured by FEV₁ at day 21 vs day 0. No significant differences were observed among the treatment groups for diary card parameters or QOL. (S)-albuterol did not appear to affect the clearance of (R)-albuterol. In a subset of patients with severe asthma, a dose-response relationship was observed for LEV, indicating that higher doses were more effective.

Conclusions. LEV had bronchodilator activity comparable to 4- to 8-fold higher doses of RAC and also demonstrated a slightly better safety profile. LEV should be used as the starting dose in 4- to 11-year-old children with asthma. Patients with more severe asthma might benefit from higher doses.

Reviewer’s Comments. The more favorable therapeutic index for LEV is certainly a valuable feature in children with overtly poor tolerance of RAC and deserves a trial in any child with more severe disease, where response to RAC is suboptimal. There is some suggestion that LEV would be more cost-effective in the hospital setting if it allows for less frequent dosing, as has been claimed. Factors mitigating against the empiric use of LEV first-line, especially at home, include the following: most children overtly tolerate RAC well; AEs noted are generally benign; no MDI form of LEV currently exists; there is a short storage time once a package is opened; and LEV costs much more.

JAMES R. BANKS, MD
Arnold, MD

β₂-Agonist Tolerance and Exercise-Induced Bronchospasm


Purpose of the Study. Tolerance to the bronchoprotective effects of β₂-agonists after regular use has been demonstrated by a number of groups. These authors asked whether patients receiving scheduled β₂-agonist had a decrease in response to rescue use of β₂-agonist when bronchospasm is induced by a “natural” stimulus, exercise. Thus, they were looking for loss of the bronchodilator response rather than loss of protection to bronchoconstriction.

Study Population. Adults aged 18 to 50 years with a history of exercise-induced wheezing and a drop of forced expiratory volume in 1 second (FEV₁) by at least 15% after exercise challenge. Subjects could have no interfering disease and could not be receiving >1500 μg/day beclomethasone or equivalent.

Methods. Subjects withheld β₂-agonist for 8 hours before testing (36 hours for long-acting β₂-agonists). The qualifying bicycle ergometer challenge used an incremental increase in workload till the subject could not continue. A 15% fall in FEV₁ was required for study entry. Before and after 1 week of study treatment, subjects performed dry-air exercise challenge at 80% of the demonstrated maximum workload for 7 minutes with an additional 1-minute dry air inhalation. Spirometry was repeated at 1, 3, and 5 minutes after exercise, then inhaled albuterol rescue was given and spirometry repeated at 10, 15, 20, and 25 minutes. The study treatments were albuterol via metered-dose inhaler (MDI) 2 puffs four times a day (QID) for 1 week, or matching placebo, given in double-blind crossover fashion with no washout between treatment weeks. During the treatment week, rescue for symptoms was limited to ipratropium.

Results. Of 22 patients screened, 9 were randomized (8 female, age: 18–44). The mean standard deviation (SD) forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) ratio was 83%. Compared with the placebo week, after the week of albuterol treatment, the onset of bronchoconstriction was sooner, with a 90% greater fall in FEV₁ at 5 minutes, although the baseline FEV₁ for the groups was similar. The final FEV₁ after albuterol rescue was significantly lower in the treated than placebo group, but the change in FEV₁ from its nadir was similar for the 2 groups, ie, the response curves were parallel.

Conclusions. Scheduled short-acting bronchodilator use leads to increased bronchoconstriction after exercise and suboptimal response to rescue albuterol after exercise.

Reviewer’s Comments. Although the subjects are young adults, the results are probably applicable to children with asthma. The question of tachyphylaxis to β₂-agonists has been argued for 2 decades, at least. Large clinical trials generally have not suggested significant risk to frequent β₂-agonist use, but numerous studies show at least partial loss of bronchoprotective effects with routine use of β₂-agonists. Such studies have supported the recent tendency to reserve short-acting β₂-agonists for symptom relief. This study further justifies this restrictive approach to short-acting β₂-agonists. However, the mechanism by which the increased exercise response is generated is still unclear. The authors suggest that the effect is attributable to β₂-receptor downregulation, because the earlier onset of bronchoconstriction in the albuterol group would be consistent with lack of bronchoprotection from endogenous catecholamines. The alternative explanation of increased airway inflammation associated with routine β₂-agonist use is not thought likely by the authors because the FEV₁ was similar at baseline. An interesting study to help tease out the mechanism would add levalbuterol as a study treatment, because studies suggest it, unlike racemic albuterol, is not associated with increased methacholine sensitivity after scheduled treatment.

LARRY W. WILLIAMS, MD
Durham, NC

1-Year Efficacy and Safety of Inhaled Formoterol Dry Powder in Children with Persistent Asthma


Purpose of the Study. Previous published studies in adults and children have shown the addition of long-acting β-agonists to low- to medium-dose inhaled corticosteroids provided symptom relief and pulmonary function improvement greater than doubling the dose of inhaled corticosteroids alone. This study investigated the 12-month efficacy and safety of 2 doses of formoterol dry powder capsules for inhalation in children receiving antiinflammatory therapy and still requiring daily administration of short-acting β-agonists for symptom relief.
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James R. Banks
Pediatrics 2003;112;480

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