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The effect of stepping down combination therapy on airway hyperresponsiveness to mannitol

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Summary
Rationale: Controversy exists about the safety of long acting beta2-agonist (LABA) treatment, in particular in children. Combination therapy with a LABA and an inhaled corticosteroid (ICS) is prescribed to children with moderate asthma and can be stepped down by withdrawal of the LABA when asthma is well controlled.
Objective: To analyze the effect of stepping down from LABA/ICS combination therapy to monotherapy with the same dose of ICS on the airway response to mannitol in asthmatic children.
Methods: 17 children, aged 12–17 years, with clinically stable asthma, receiving combination therapy, were analyzed in this observational prospective open-label study. Children performed a mannitol challenge at baseline and 30 ± 4 days after their medication was stepped down to ICS monotherapy. The changes in the provoking dose of mannitol to cause a 15% fall in FEV_1 (PD_{15}), response-dose ratio and recovery time following a short acting beta2-agonist to $\geq$95% of baseline FEV_1 were assessed.
Results: Mannitol PD_{15} and response-dose ratio did not significantly change after stepping down. The recovery time following a short acting beta2-agonist to $\geq$95% of baseline FEV_1 was significantly shorter ($p = 0.01$) after the withdrawal of the LABA.

Abbreviations: CI, Confidence Interval; FeNO, Fraction of exhaled Nitric Oxide; FEV_1, Forced Expiratory Volume in 1 s; ICS, Inhaled Corticosteroid; LABA, Long Acting Beta2-Agonist; PD_{15}, Provoking Dose to cause a 15% fall in FEV_1; SABA, Short Acting Beta2-Agonist; SD, Standard Deviation.

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Conclusions: In short-term follow-up, stepping down clinically stable asthmatic children from combination therapy to monotherapy with an ICS does not change airway hyperresponsiveness (AHR) to mannitol but does shorten recovery time to baseline lung function following a rescue short acting beta2-agonist.

Introduction

Clinical guidelines recommend to step up asthma therapy when asthma is not well controlled on a low to moderate dose of inhaled corticosteroids (ICS).[1,2] In adults the addition of a long acting beta2-agonist (LABA) leads to better asthma control than increasing the dose of ICS.[3] In children however, combination therapy did not lead to a significant reduction, but rather a trend towards an increased risk of asthma exacerbations and hospital admissions.[3] These trends raised concern about the safety of combination therapy in children and questions on whether and when the LABA should be withdrawn when stepping down from combination therapy. The suggested step down approach by current guidelines for asthmatic adults is to reduce the ICS to the lowest dose possible, while continuing the LABA.[1,2] An alternative approach, that was recently suggested by the US Food and Drug Administration, is to discontinue the LABA once asthma control is achieved and continue the ICS at the same dose.[4]

In a recent study in asthmatic adults by Reddel et al., both step down approaches were compared, and found to result in no significant difference in FEV_1, rescue bronchodilator use, methacholine PD_{20}, sputum eosinophils and FeNO.[5] However, moderate exacerbations were less frequent and subjects could be titrated to a lower dose of ICS in subjects with combination therapy.[5] Previous studies in asthmatic adults comparing both step down approaches found a deterioration of morning peak expiratory flow, daily symptoms and bronchodilator use in subjects who's LABA was withdrawn.[6–8] The effect of withdrawal of the LABA from combination therapy on airway hyperresponsiveness (AHR) in children has not been extensively studied.

Regular use of short acting beta2-agonists (SABAs) and LABAs leads to downregulation and desensitization of the beta2-adrenoreceptor,[9] which affects AHR in several ways. Firstly, it results in a reduced bronchodilator effect of rescue SABA treatment in circumstances of acute bronchoconstriction: bronchodilator tolerance. Bronchodilator tolerance develops after a single dose of a LABA and reaches a maximum after 1 week of regular treatment.[10] It leads to a prolonged recovery time after bronchoconstriction and the need for extra doses of rescue medication.[10–14] Simultaneously, regular use of LABAs leads to a reduced protection against AHR provoked by natural or administered stimuli, such as methacholine,[15,16] allergen[16] and exercise.[17] This is called bronchoprotective tolerance. Furthermore, Hancox et al. have shown that regular use of SABAs can even enhance AHR to exercise.[12]

In this study, we analyzed the effect of stepping down clinically stable asthmatic children from LABA/ICS combination therapy to ICS monotherapy on AHR to mannitol. Our hypothesis was that the withdrawal of the LABA would lead to a decrease in AHR to mannitol.

Methods

Subjects

Children with mild to moderate asthma, treated with LABA/ICS combination therapy, who underwent a medication reduction according to treatment guidelines,[1,2] were screened. Twenty four children with mild to moderate, clinically stable asthma for >3 months (i.e. no hospital admissions or use of systemic corticosteroids), aged 12–17 years, were asked to participate in this study. The study was approved by the Medical Ethics Committee, Enschede. All children and parents gave written informed consent.

Study design

This was an observational, prospective open-label study. Children and their parents were contacted four and two weeks prior to the first visit to emphasize on the importance of medication adherence. During the first visit to the outpatient clinic, all children were interviewed about medication use and adherence by the lung function assistant. They performed a set of tests, including a mannitol challenge, measurement of Fraction of exhaled Nitric Oxide (FeNO) and an asthma control test. After the first visit treatment was stepped down to ICS monotherapy. The second visit was scheduled 30 ± 4 days after the first visit. During the second visit the same set of tests was performed. Primary outcome was change in the provoking dose of mannitol required to cause a 15% fall in FEV_1 (PD_{15}). Secondary outcomes were changes in mannitol response-dose ratio, recovery time to $\geq$95% of baseline FEV_1 following a rescue SABA, FeNO and scores on the asthma control test.

Spirometry

A MicroLoop® MK8 Spirometer (Micromedical, Quayside, United Kingdom) was used to measure pulmonary volumes and flow-volume loops. All spirometric measurements were performed in duplicate using a standard protocol.[18]

Mannitol challenge

The mannitol challenge was performed according to the standard laboratory protocol, using the commercially available mannitol test kit (Aridol®, Pharmaxis, Frenchs Forest, Sydney, Australia).[19] Children were required to withhold the use of leukotriene antagonists, intranasal steroids, LABAs and ICSs for 24 h and SABAs for 8 h before both mannitol challenges. No vigorous exercise was permitted for 8 h before a mannitol challenge.