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

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KEYWORDS
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Long acting beta2-agonist;
Adolescents

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.

The dose protocol consisted of 0, 5, 10, 20, 40, 80, 160, 160 and 160 mg mannitol. Children were asked to exhale completely before taking a calm deep inspiration from the device and subsequently hold their breath for 5 s. Children were asked to exhale through their mouth to minimize deposition in the nasopharynx. FEV_1 was measured 60 s after each dose of mannitol. The challenge ended when $a \geq 15\%$ fall in FEV_1 from baseline or $a \geq 10\%$ fall between subsequent doses occurred, or the cumulative dose of 635 mg mannitol had been administered. Mannitol PD_{15} was calculated by linear interpolation. The response-dose ratio was calculated by taking the final percent fall in FEV_1 recorded and dividing it by the cumulative dose of mannitol administered.

After the challenge, children received a dose of 100 μg Salbutamol and FEV_1 was measured at $t = 1, 3, 5, 10, 15$ and 20 min until lung function had returned to $\geq$95% of baseline FEV_1. If FEV_1 had not recovered to $\geq$95% of baseline after 10 min, children received a second dose of 100 μg Salbutamol.

Fraction of exhaled nitric oxide

The single-breath online measurement method was used to measure FeNO before any forced expiratory maneuvers.[20] Children were asked to exhale to residual volume and then inhale NO-free air through a hand-held nitric oxide analyzer (Niox Mino®, Aerocrine, Stockholm, Sweden). Children inhaled near to total lung capacity and immediately exhaled at a constant flow rate of 50 ml/s. FeNO was measured in the expired air by its reaction with ozone, which is detected by chemiluminescence.

Asthma control test

The asthma control test is a 5 item survey assessing asthma symptoms (daytime and nocturnal), use of rescue medications and the effect of asthma on daily functioning. Each item includes 5 response options corresponding to a 5-point scale. The total score ranges from 5 points (uncontrolled asthma) to 25 points (well controlled asthma).

Statistical analysis

Statistical analysis was performed with SPSS Statistics® version 17.0 for Windows®. Best values of spirometric measurements of FEV_1 were used for statistical calculations. Geometric means ±95% confidence intervals (CI) of mannitol PD_{15} and response-dose ratio were calculated using the log-transformed values. Recovery time was expressed as mean time to reach $FEV_1 \geq 95\%$ of baseline. Recovery curves were analyzed as the total area under the curve. FeNO values were analyzed before and after natural log transformation. Within group changes were analyzed with a paired t-test or Wilcoxon-signed rank sum test, as appropriate. Spearman's rank correlation coefficient was calculated for the correlations between FeNO, scores on the asthma control test, FEV_1, PD_{15} and response-dose ratio. The difference between the number of children positive on both mannitol challenges was analyzed with a McNemar test. Statistical significance was defined as $p < 0.05$.

Results

Subjects

Twenty children were included, 17 of which completed the study. In 3 children, the first mannitol challenge was terminated before they reached $a \geq 15\%$ fall in FEV_1. One subject was excluded because she was unable to perform reproducible expiratory flow-volume curves. One subject

Table 1 Baseline characteristics of research population ($N = 17$).

	Gender	Age	Med	Daily dose ICS (μg)	LTRA	Baseline FEV_1 (% pred.)		PD_{15} mannitol (mg)	
						ICS/LABA	ICS	ICS/LABA	ICS
1	M	11	FP/SAL	200	−	104	98	>635	268
2	M	13	BUD/F	400	+	75	80	144	217
3	M	14	FP/SAL	100	−	85	89	>635	>635
4	M	13	FP/SAL	250	−	94	101	145	419
5	V	13	BUD/F	200	+	96	83	114	36
6	V	12	BUD/F	400	−	100	100	139	169
7	M	12	BUD/F	200	−	78	73	150	291
8	V	14	FP/SAL	250	−	96	86	>635	256
9	M	14	FP/SAL	200	−	104	81	132	66
10	V	13	FP/SAL	200	−	68	82	49	115
11	M	13	BUD/F	200	+	84	91	236	241
12	V	13	FP/SAL	500	−	98	108	308	467
13	M	17	BUD/F	400	−	69	61	255	58
14	M	13	FP/SAL	200	+	101	97	>635	>635
15	M	13	BUD/F	400	−	76	91	250	221
16	M	13	FP/SAL	200	−	120	122	367	409
17	V	15	FP/SAL	200	+	117	120	>635	>635

BUD/F = budesonide/formoterol; FEV_1 = forced expiratory volume in 1 s; FP/SAL = fluticasone propionate/salmeterol; ICS = inhaled corticosteroid; LABA = long acting beta2-agonist; LTRA = leukotriene receptor antagonist; PD_{15} = provoking dose to cause a 15% fall in FEV_1.

Table 2 Changes in outcome parameters.

	LABA/ICS combination therapy	ICS monotherapy	*p*-value
FEV_1 (% pred.)	92.1 ± 15.6	91.9 ± 15.7	0.96
PD_{15} (mg)	168.9 (56.9, 501.9)	183.7 (38.2, 884.9)	0.91
RDR (% fall in FEV_1/mg)	0.05 (0.01, 0.36)	0.06 (0.01, 0.54)	0.81
Asthma control test	20.2 ± 4.7	20.8 ± 4.7	0.10
FeNO (ppb)	35.5 ± 27.6	36.6 ± 26.5	0.39
Recovery time to ≥95% of baseline FEV_1 (min)	9.9 ± 6.2	5.7 ± 4.3	**0.01**
Area under the curve (% min)	1908.9 ± 66.5	1944.2 ± 51.4	**0.04**

Data expressed as mean ± standard deviation (SD) or Geometric mean (95% CI). 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; RDR = Response-Dose Ratio.

experienced a frequent and persistent cough after the 5th dose step, which interfered with the fixed time schedule and one subject was unwilling to continue after the 8th dose step because she didn't like the taste of mannitol. Patient characteristics are presented in Table 1.

Before the first mannitol challenge children reported an average use of 1.8 puffs of SABAs per week (including pre-exercise use) and a mean medication adherence of 81 ± 15% during the past 4 weeks. After the medication reduction children reported an average use of 1.6 puffs of SABAs per week and an adherence of 82 ± 12%. Changes in all outcome parameters are shown in Table 2.

Spirometry

Baseline FEV_1 before the first mannitol challenge had a normal distribution with a mean (±SD) of 92.1 ± 15.6% predicted value, which was not significantly different from baseline FEV_1 before the second challenge (91.9 ± 15.7% predicted value, $p = 0.96$).

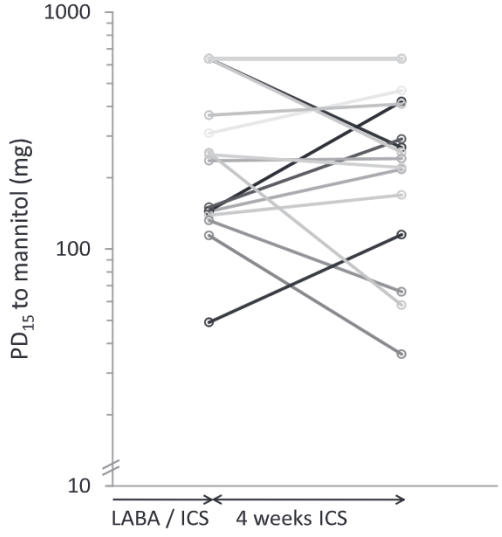

Figure 1 Individual changes in Mannitol PD_{15} (mg) after regular treatment with LABA/ICS combination therapy and 4 weeks after stepping down to ICS monotherapy. ICS = inhaled corticosteroid; LABA = long acting beta2-agonist; PD_{15} = provoking dose to cause a 15% fall in FEV_1.

Mannitol challenge

Twelve children (70.6%) were positive on the first mannitol challenge, defined by a fall in $FEV_1 \geq 15\%$ after a cumulative dose of ≤635 mg mannitol. Fourteen children (82.4%) were positive on the second challenge. The number of children positive on a mannitol challenge was not significantly different between both tests ($p = 0.50$). Geometric mean for the PD_{15} for children positive on the first challenge was 168.9 mg (95% CI: 56.9—501.9) and for the second challenge 183.7 mg (95% CI: 38.2—884.9), which was not significantly different ($p = 0.91$; Fig. 1).

Mean maximum percent fall in FEV_1 (±SD) after the first challenge was 15.6 ± 5.4% after a mean cumulative dose (±SD) of 347 ± 215 mg mannitol. After the second challenge FEV_1 fell 15.6 ± 4.6% after a cumulative dose of 331 ± 196 mg. Geometric mean of the response-dose ratio did not change after the medication reduction ($p = 0.81$).

Children using leukotriene antagonists did not have a different response to mannitol than children not using these medications.

Recovery

Mean [Range] recovery time following a SABA was 9.9 min [1—20] after the first mannitol challenge and 5.7 min [0—15] after the second challenge, which was significantly shorter ($p = 0.01$; Fig. 2). Six children needed a second dose of 100 μg Salbutamol after the first challenge and only one child after the second challenge. Recovery time after mannitol was not age dependent. The total area under the recovery curve (±SD) was also significantly larger after the second challenge (1908.9 ± 66.5% min vs. 1944.2 ± 51.4% min, $p = 0.04$).

Fraction of exhaled nitric oxide

There was no significant difference in FeNO measured before both challenges (35.5 ± 27.6 vs. 36.6 ± 26.5 ppb; $p = 0.39$; Fig. 3). There was no correlation between FeNO and mannitol PD_{15} or response-dose ratio.

Asthma control test

There was no significant difference between symptom scores on the asthma control test after the medication

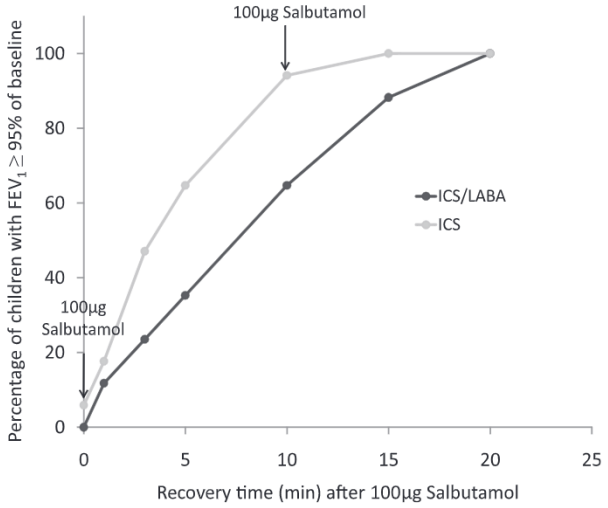

Figure 2 Percentage of patients with FEV_1 recovered to $\geq$95% of baseline after 100 µg Salbutamol at resp. 0 and 10 min after a mannitol challenge. ICS = inhaled corticosteroid; LABA = long acting beta2-agonist.

reduction (20.2 ± 4.7 vs. 20.8 ± 4.7 points, $p = 0.10$). There was no correlation between scores on the asthma control test and baseline FEV_1, FeNO, mannitol PD_{15} and response-dose ratio.

Discussion

In this study, we monitored stepping down from LABA/ICS combination therapy to ICS monotherapy in clinically stable asthmatic children. The withdrawal of the LABA did not change baseline FEV_1, ACT score, FeNO or SABA use. There was no difference in Mannitol PD_{15} and response-dose ratio. However, with LABA/ICS combination therapy there was a delayed recovery after the administration of a SABA and more children needed a second dose of SABA to recover compared to ICS monotherapy.

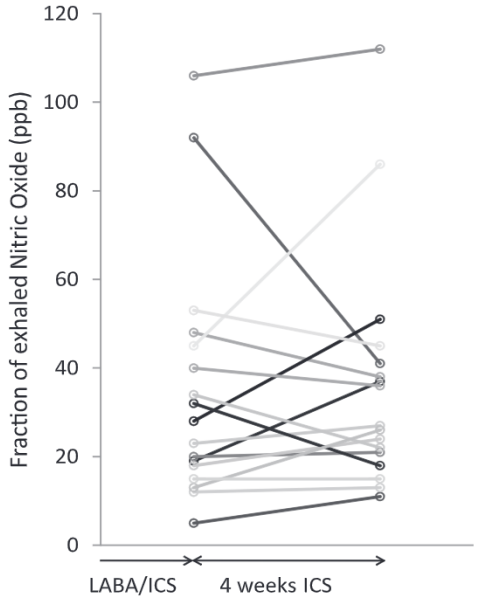

Figure 3 Individual changes in Fraction of exhaled Nitric Oxide (ppb) after regular treatment with LABA/ICS combination therapy and 4 weeks after stepping down to ICS monotherapy. ICS = inhaled corticosteroid; LABA = long acting beta2-agonist.

To our knowledge, the effect of stepping down treatment from combination therapy to ICS monotherapy on AHR to mannitol has not yet been studied in asthmatic adults or children. Previous studies in asthmatic adults compared stepping down to ICS monotherapy to stepping down to a lower dose of combination therapy.[6–8] They found a deterioration of asthma control, as measured by peak expiratory flow, daily symptom scores and SABA use in subjects whose LABA was withdrawn. However, the effect on airway inflammation, asthma exacerbations, hospitalizations and mortality was not assessed, while the main concerns with LABA treatment focus on these outcome measures.[4] A recent study in adults compared both step down approaches and found no significant difference in FEV_1, rescue bronchodilator use, methacholine PD_{20}, sputum eosinophils, FeNO and annual rate of severe exacerbations.[5] However, recently particular concern has risen about the risk of LABA treatment among children. A Cochrane review comparing step up therapy by adding a LABA to increasing the dose of ICS found that in children combination therapy led to a trend towards an increased risk of asthma exacerbations and hospital admissions.[3] The effect of different approaches to step down combination therapy in children has not been extensively studied. In a study design similar to this study the AHR to exercise (defined as % fall in FEV_1) in asthmatic children diminished after the withdrawal of the LABA,[21] suggesting an increased AHR to exercise in children on combination therapy.

Several mechanisms could contribute to the increased risk for asthma exacerbations and hospitalizations with regular use of LABAs[22]; such as the development of bronchodilator tolerance, an increased AHR to allergen, interaction with corticosteroid receptors, masking of symptoms and altered mucociliary clearance.[23] In this study, recovery time from bronchoconstriction after rescue therapy with a SABA was significantly longer after long-term use of LABA/ICS combination therapy. A prolonged recovery time after stepping up treatment with a LABA has been described in both adults and children after histamine,[11] exercise[13] and methacholine[10,14] challenges. The mechanism by which tolerance develops is not fully unraveled, but is well known that prolonged exposure to agonists desensitizes G-protein-coupled receptors, such as the beta2-adenoceptor. The principal mechanism of desensitization is cyclic-AMP-dependent and -independent phosphorylation of the receptor, which results in a limitation of receptor function. After more prolonged exposure to an agonist, an internalization of receptors occurs and the total transit time for the recycling of receptors is increased, which results in a net loss of receptors on the cell membrane (downregulation). Eventually, there is a breakdown of receptors which can only be replaced by synthesis of new receptors through transcription of the beta2-receptor gene.[9,24]

The downregulation and desensitization of the beta2-adrenoreceptor result in a decreased response to rescue SABA treatment in circumstances of acute bronchoconstriction.

The process of desensitization differs in different types of cells, which may be explained by a variation in the receptor reserve between tissues and a differential resensitization rate. Mast cells appear to desensitize more rapidly than smooth muscle cells.[9] Therefore, tolerance might be more profound against indirect bronchoprovocational stimuli, such as mannitol, that act on inflammatory cells (such as mast cells), than against direct stimuli, such as methacholine, that act directly on airway smooth muscle cells.[25]

The response to mannitol in asthmatics is supposed to mimic the airway response to exercise, as both increase the osmolarity of the airway surface liquid, triggering mediator release from mast cells. In a previous study by our study group the AHR to exercise in asthmatic children decreased after combination therapy was stepped down to ICS monotherapy.[21] We therefore expected a similar reduction in AHR to mannitol, which did not occur. We speculate that this discrepancy in results could be explained by differences in the physical responses to exercise and mannitol. Mannitol is primarily deposited in the conducting airways, because of its particle size,[26] while exercise induced hyperpnoea can dehydrate the peripheral airways as well.[27] The amount of mast cells is greater in smaller airways,[28] where only a small part of the inhaled mannitol powder will penetrate. Therefore, a change in responsiveness in the small airways due to desensitization of mast cells is more likely to be detected with an exercise challenge. Secondly, the rate of change in osmolarity, which is suggested to be a determinant of AHR,[29] may be important. This rate is likely to be slower with a mannitol challenge which is performed according to a stepwise protocol with increasing doses. Thirdly, the fall in FEV_1 after exercise is usually greater than after mannitol, because a mannitol challenge ends when FEV_1 falls $\geq$15%. Wraight et al. demonstrated that, in the same patient, the effect of tolerance becomes more apparent with increasing degrees of bronchoconstriction.[30] Therefore the effect of tolerance might have been more apparent after an exercise challenge compared to a mannitol challenge.

Several limitations of this study need to be addressed. Firstly, there was no control group in whom we did not change the medication regimen, making this study susceptible to bias due to an improved adherence. We measured adherence by interviewing the children and found no difference in reported adherence before both challenges. Secondly, although all children used combination therapy, they were prescribed different medication regimens and different doses of ICSs. Five children were using leukotriene antagonists (LTRA), which are known to shorten recovery time following mannitol.[31] We found no significant difference in recovery time for children on LTRA compared to children not on LTRA. Thirdly, we only measured short term effects of the withdrawal of the LABA and therefore could not study long term outcomes, such as asthma exacerbations and hospitalizations.

A long recovery time and tolerance to a rescue bronchodilator are likely to affect children in daily life, as they compromise their athletic performance and participation in active play and sports with peers. Failure to respond to rescue bronchodilators could offer a possible explanation for the association between LABA use and asthma related intubations and mortality. Theoretically, bronchodilator tolerance could be overcome by increasing the dose of SABAs, which has happened in the last decades in treatment of acute exacerbations. However, Haney and Hancox found that the response to high dose nebulised salbutamol was still 15% lower after regular formoterol compared to placebo.[32]

This study shows that in short-term follow-up (one month), stepping down clinically stable children from LABA/ICS combination therapy to ICS monotherapy did not change AHR to mannitol and FeNO and did not alter asthma control as measured by spirometry, SABA use and ACT score. The withdrawal of the LABA led to a significantly shorter recovery time following a rescue SABA after a mannitol challenge, suggesting a reversal of previously developed bronchodilator tolerance. Future studies should be directed at the longer term effects of different step down approaches from combination therapy in asthmatic children.

Conflict of interest

The authors have no conflicts of interest.

Acknowledgements

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