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Can the response to a single dose of beclomethasone dipropionate predict the outcome of long-term treatment in childhood exercise-induced bronchoconstriction?

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Abstract

Background: Exercise-induced bronchoconstriction (EIB) is a frequent and highly specific symptom of childhood asthma. Inhaled corticosteroids (ICS) are the mainstay of controller therapy for EIB and asthma; however, a proportion of asthmatic children and adolescents is less responsive to ICS. We hypothesized that a single dose response to ICS could function as a predictor for individual long-term efficacy of ICS.

Objective: To assess the predictive value of the bronchoprotective effect of a single-dose beclomethasone dipropionate (BDP) against EIB for the bronchoprotective effect of 4 weeks of treatment, using an exercise challenge test (ECT).

Methods: Thirty-two steroid-naïve children and adolescents aged 6 to 18 years with EIB were included in this prospective cohort study. They performed an ECT at baseline, after a single-dose BDP (200μg) and after 4 weeks of BDP treatment (100 μg twice daily) to assess EIB severity.

Results: The response to a single-dose BDP on exercise-induced fall in FEV1 showed a significant correlation with the response on exercise-induced fall in FEV1 after 4 weeks of BDP treatment ($r = .38$, $p = .004$). A reduction in post-exercise fall in FEV1 of more than 8% after a single-dose BDP could predict BDP efficacy against EIB after 4 weeks of treatment with a positive predictive value of 100% (CI: 86.1–100%) and a negative predictive value of 29.4% (CI: 11.7%–53.7%).

Conclusion: We found that the individual response to a single-dose BDP against EIB has a predictive value for the efficacy of long-term treatment with BDP. This could support clinicians in providing personalized management of EIB in childhood asthma.

KEYWORDS
Asthma, exercise challenge test, exercise-induced bronchoconstriction, inhaled corticosteroids, pediatric, spirometry

Abbreviations: (C)-ACT, (Childhood) asthma control test; BDP, beclomethasone dipropionate; BMI, body mass index; ECT, exercise challenge test; EIB, exercise-induced bronchoconstriction; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; MDI, metered dose inhaler; SABA, short-acting B-agonist.

1 | INTRODUCTION

Asthma is a common childhood disease that is characterized by chronic inflammation of the airways. This causes bronchial hyperreactivity with episodic expiratory airflow limitation, leading to respiratory symptoms such as cough, wheeze, shortness of breath and chest tightness.[1] Exercise-induced bronchoconstriction (EIB) is a frequent and persistent symptom of childhood asthma that can prevent children and adolescents from participating in sports and play and negatively impacts the quality of life.[2-4]

Inhaled corticosteroids (ICS) are the mainstay of controller therapy in asthmatic children and adolescents as they reduce airway inflammation and provide long-term bronchoprotection.[1,5] ICS are generally considered safe, but there are potential adverse systemic effects of long-term use such as growth retardation and adrenal suppression.[6-8] Asthma is a heterogeneous disease and clinical phenotypes are highly variable, which is exemplified by the variability of patients' responses to medication.[9-13] There is a group of asthmatic children and adolescents who are less responsive to ICS and who are often treated with high doses of ICS.[14-20] Prevalence of non-responsiveness to ICS in the literature varies highly and ranges from 5 to 60%, depending on the definition of responsiveness.[11,14-21] Several biomarkers, such as exhaled nitric oxide levels, total eosinophil count and IgE levels, are associated with a positive ICS response. Although there are biomarkers that can assess treatment effects,[22,23] there is currently no biomarker used in routine clinical practice that can accurately predict individual ICS responsiveness before treatment in asthmatic children or adolescents.[1,11,24,25]

Previous studies demonstrated a significant acute effect of a single (high and low) dose ICS on bronchial responsiveness measured by an indirect bronchial provocation test.[26-30] This single-dose effect showed a variability similar to the variability observed in long-term treatment.[30] We, therefore, hypothesized that the individual single dose response to ICS could function as a non-invasive predictor for the individual effectiveness of ICS treatment after 4-week treatment. This could be helpful to personalize treatment and prevent inappropriate long-term therapy and/or escalation of therapy.

The aim of this study was to assess the predictive value of the bronchoprotective effect of a single-dose beclomethasone dipropionate (BDP) against EIB for the bronchoprotective effect of 4 weeks of treatment, using an exercise challenge test (ECT).

Key Message

In this paper, we show that the bronchoprotective effect to a single dose of inhaled corticosteroids in children and adolescents with asthma has a predictive value for the bronchoprotective effect of 4-week treatment. This is relevant because it offers opportunities for personalizing asthma treatment.The response to a single-dose beclomethasone dipropionate (BDP) against exercise-induced bronchoconstriction (EIB) has a predictive value for long-term efficacy. An improvement in fall in post-exercise FEV1 of more than 8% after a single-dose BDP compared with baseline could predict BDP efficacy against EIB after 4 weeks of treatment. This could support clinicians in providing personalized management of EIB in childhood asthma.

2 | MATERIALS AND METHODS

2.1 | Study design

This cohort study had a prospective, open-label design. During a baseline visit, participants performed a standardized ECT. A second ECT was performed within 2 weeks after baseline visit and 6 h after a first dose of 200 μg BDP. After this ECT, they continued using a therapeutic dose of BDP 100 μg twice daily, and after 4 weeks of treatment, a third ECT was performed. Participants used either a pressurized metered dose inhaler (MDI) with an aerochamber or a breath-actuated MDI, based on an instruction session with the asthma nurse. Before starting the ECT, participants completed the Childhood Asthma Control Test (C-ACT) or Asthma Control Test (ACT) (when, respectively, 4 to 11 or over 12 years of age) at baseline and at the final study visit.[31,32]

2.2 | Participants

Forty children and adolescents were recruited from the outpatient paediatric clinic of Medisch Spectrum Twente, Enschede, the Netherlands, between May 2019 and September 2021. Steroid-naïve children and adolescents aged 6–18 years with paediatrician diagnosed asthma who were planned to start on BDP for clinical reasons were screened by a standardized ECT. In- and exclusion criteria are described in Table 1. The study was approved by the Medical Ethics Committee of Medisch Spectrum Twente, Enschede. All participants and their parents/guardians received written patient information and provided written informed consent prior to participating in this study.

2.3 | Exercise challenge test

Exercise challenges were performed in a climate chamber with dry, cold air (10.0–12.0°C), according to the standards of the American Thoracic Society.[33] Children aged 6 to 8 years old exercised on a jumping castle[34] and children or adolescents aged 8 years and older ran on a treadmill with an incline of 10%. They exercised for 6 min at 80% of predicted maximal heart rate. Pulmonary function was measured using the standard European Respiratory Society Protocol.[35,36] Lung function was measured with a MicroLoop® spirometer before exercise and at 1, 3 and 6 min post-exercise or until FEV1 stopped declining. Afterwards, participants received 200 μg salbutamol and spirometry measurements were repeated. Exercise-induced

TABLE 1 In- and exclusion criteria of study protocol

Inclusion criteria	Exclusion criteria
-Age 6–18 years	-Baseline FEV1 < 70%
-Paediatrician diagnosed asthma	-Inability to perform an ECT including spirometry
-Clinical reason to start BDP	-Use of nasal, systemic or inhaled corticosteroids, antihistamines, cromoglycates, anticholinergics or leukotriene antagonists in two weeks prior to the study
	-Changes in asthma medication during the study period
	-Upper or lower respiratory tract infection during study period

Abbreviations: BDP: Beclomethasone dipropionate; ECT Exercise Challenge Test; FEV1: Forced Expiratory Volume in 1 s.

bronchoconstriction was assessed for each individual child by the following calculation: *Post-exercise fall in FEV1* = $(FEV1_{pre\text{-}exercise} - FEV1_{post\text{-}exercise})/FEV1_{pre\text{-}exercise} * 100\%$. A post-exercise fall in FEV1 of >10% was classified as positive for EIB.[37]

2.4 | Responders

The relative decrease in post-exercise fall in FEV1 was calculated for the third ECT compared with baseline ECT: *Relative difference in fall in FEV1* = $(Fall\ in\ FEV1_{baseline} - Fall\ in\ FEV1_{4\ weeks\ BDP\ treatment}\ /Fall\ in\ FEV1_{baseline}$. Children and adolescents with a relative decrease in fall in FEV1 of ≥25% after 4 weeks of BDP treatment were classified as responders[30,38,39]

2.5 | Statistical analysis

Normality of data was visually inspected. Descriptive results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (interquartile range) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal. Normality could not be assumed for the non-responder group due to the small group size. For interpretability, data that followed a normal distribution in the responder group were also presented with mean (SD) for the non-responder group. Characteristics between responders and non-responders were compared with Fisher's exact test (binary variables) or the Mann–Whitney U test (continuous variables). Missing data were handled by pairwise deletion.

The primary endpoint was the correlation between the difference in post-exercise fall in FEV1 between a baseline ECT and an ECT after a single-dose BDP and between a baseline ECT and an ECT after 4 weeks of BDP treatment reported as an intraclass correlation coefficient.

Differences between baseline FEV1 at the first, second and third ECT, and between percentages of post-exercise fall in FEV1 at the first, second and third ECT, were analysed with mixed model repeated measurements analyses. A cross-tabulation was made of responders and non-responders to a single-dose BDP and responders and non-responders after 4 weeks of BDP treatment. A receiver operating characteristic curve was used to define an optimal set point for the absolute reduction in fall in FEV1 after a single dose to predict a good response to BDP after 4 weeks of treatment. An optimal set point was defined as a high specificity with acceptable sensitivity to obtain a high positive predictive value. A cross-tabulation was made of responders to a single-dose BDP using this set point and responders after 4 weeks of BDP treatment, and McNemar's test was used to determine the significance of the association in this cross-tabulation.

IBM SPSS Statistics 26 was used for statistical analysis. A 2-sided value of $p < .05$ was considered statistically significant.

2.6 | Sample size calculation

Based on the fact that we regarded a correlation coefficient between the fall in FEV1 after a single-dose BDP and the fall in FEV1 after 4 weeks of BDP treatment of less than 0.65 as not clinically relevant and an expected correlation coefficient of 0.85, we calculated a sample size of 37. A two-sided hypothesis test with a significance level of 0.05 and power of 80% was used. To account for possible drop-out, a population size of 40 was chosen.

3 | RESULTS

Thirty-seven out of forty eligible children and adolescents completed the study. Patient baseline characteristics are presented in Table 2. Two participants were excluded due to an upper respiratory tract infection during the study period. One participant was excluded since he was prescribed a course of oral prednisone during the study period due to a flare-up of his eczema. No adverse events were reported during the study period.

None of the participants used any controller asthma medication (e.g. inhaled, nasal or oral corticosteroids or montelukast) at least 4 weeks prior to inclusion. Eighty-one per cent used short-acting B-agonists (SABA) as needed. Based on baseline ECT results, 46% of children and adolescents had mild (post-exercise fall in FEV1 10%–25%), 43% moderate (post-exercise fall in FEV1 25%–50%) and 11% severe EIB (post-exercise fall in FEV1 > 50%).[37]

FEV1 prior to the first ECT (93.0% predicted, CI: 89.3%–96.6%) was not significantly different from FEV1 after a single-dose BDP (92.7%, CI: 89.0%–96.3%. $p = .993$). FEV1 after 4 weeks of BDP treatment (96.4%, CI: 92.7%–100.0%) had, however, significantly

TABLE 2 Baseline characteristics of study population ($n = 37$)

Variable	Total $n = 37$	Responders[a] $n = 32$	Non-responders[a] $n = 5$	p-value (2-sided)
Sex (% male)	28/37 (78%)	26/32 (81%)	2/5 (40%)	.081
Age (years)	9.68 ± 2.6	9.72 ± 2.5	9.40 ± 3.1	.935
Height (cm)	143 ± 14.9	143 ± 15.1	145 ± 15.3	.627
Weight (kg)	36.9 ± 11.4	36.7 ± 11.5	38.6 ± 11.6	.524
BMI Z score	0.07 ± 1.0	0.05 ± 1.0	0.17 ± 1.2	.689
Atopy[b]	29/34 (85%)[c]	27/29 (93%)[c]	2/5 (40%)	.015
Baseline FEV1 (% predicted)	93.0 ± 12.0	91.7 ± 11.3	101 ± 14.9	.620
Max % fall in FEV1	30.5 ± 13.9	32.1 ± 13.9	20.1 ± 9.4	.213
EIB severity				.388
Mild EIB	17/37 (46%)	13/32 (41%)	4 (80%)	
Moderate EIB	16/37 (43%)	15/32 (47%)	1 (20%)	
Severe EIB	4/37 (11%)	4/32 (13%)	0%	
(C-)ACT	19.0 ± 4.3	19.7 ± 4.0	17.0 ± 4.2	.220
(C)-ACT >19	15/30 (50%)	14/26 (54%)	1/4 (25)%	.598
SABA prescription	30/37 (81%)	26/32 (81%)	4/5 (80%)	1.000

Note: Data are presented as mean ± standard deviation or *n* (%).

Abbreviations: BMI: Body Mass Index; (C)-ACT: (Childhood) Asthma Control Test; EIB: Exercise-induced bronchoconstriction; FEV1: Forced Expiratory Volume in 1 s; SABA: Short-acting B-agonist.

[a]A responder is defined as ≥25% relative reduction in max. % fall in FEV1 compared with baseline after 4-week BDP treatment. Children with a relative reduction <25% after 4 weeks of BDP treatment are classified as non-responder.

[b]Atopy confirmed by chemiluminescent enzyme-labelled sequential immunoassay or skin-prick test.

[c]3/37 participants were not tested for atopy, all in the responder group.

[d]There are 7 missing baseline (C)-ACT scores: 6 in the responder group and 1 in the non-responder group.

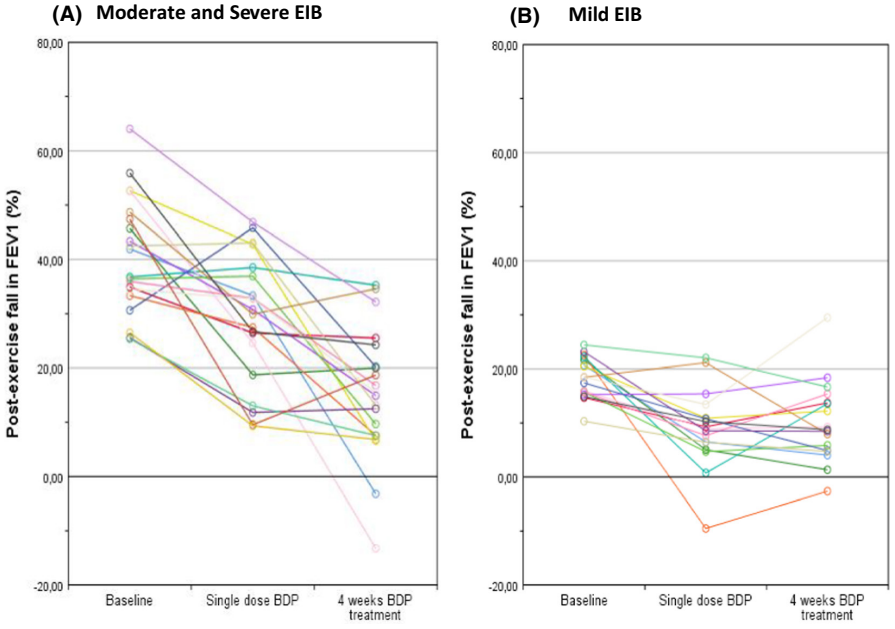

FIGURE 1 Post-exercise fall in FEV1 during an ECT at baseline, after a single dose BDP and after 4 weeks of treatment with BDP. (a) children and adolescents with moderate ($n = 16$) and severe ($n = 4$) EIB. (b) children and adolescents with mild EIB ($n = 17$)

increased compared with both FEV1 at the first ECT ($p = .023$) and FEV1 after the single-dose BDP ($p = .012$).

3.1 | Exercise-induced bronchoconstriction following BDP treatment

The individual post-exercise fall in FEV1 at the first, second and third ECT is shown in Figure 1. Mean post-exercise fall in FEV1 after the single-dose BDP (19.8%, CI: 15.1%–24.5%) had significantly decreased compared with post-exercise fall in FEV1 at baseline (30.4%, CI: 25.8%–35.1%, $p < .001$). Mean post-exercise fall in FEV1 after 4 weeks of BDP treatment (12.9%, CI: 9.4%–16.4%) had significantly decreased compared with both post-exercise fall in FEV1 at the first ECT ($p < .001$) and post-exercise fall in FEV1 after the single-dose BDP ($p = .014$).

There was a significant intraclass correlation between the response on exercise-induced fall in FEV1 to a single dose of BDP and response after 4 weeks of treatment ($r = .38$, $p = .004$) (Figure 2).

Thirty-two out of 37 (87%) participants could be considered a responder after 4 weeks of BDP treatment. The receiver operating characteristic curve (Figure 3) showed an area under the curve of 0.775 (CI 0.619–0.932). Specificity was 100% (CI: 55.0%–100%) and sensitivity 62.5% (CI: 45.0%–77.9%) for being a responder after 4 weeks of BDP treatment when a cut-off of ≥8.3% absolute reduction in fall in FEV1 after a single-dose BDP was chosen. This resulted in a positive predictive value of 100% (CI: 86.1%–100%) and a negative predictive value of 29.4% (CI: 11.7%–53.7%). The cross-tabulation is shown in Table 3.

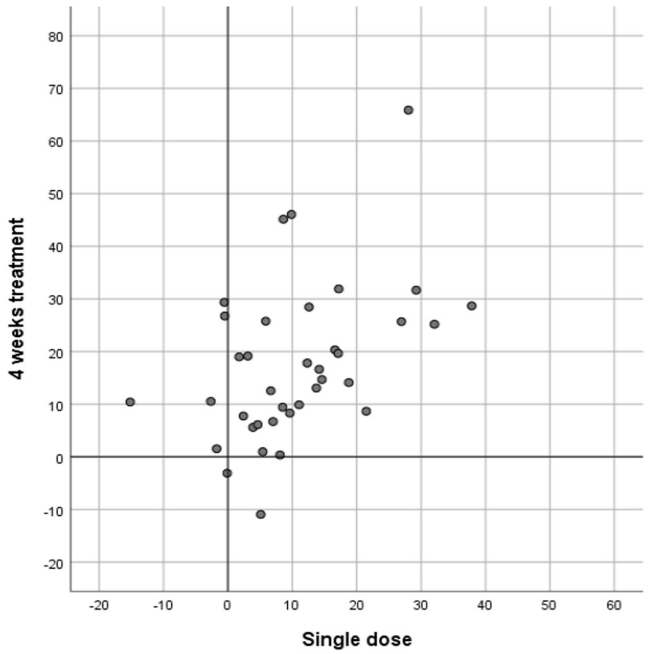

FIGURE 2 Difference in post-exercise fall in FEV1 between a baseline ECT and an ECT after a single dose BDP (100 μg) and between a baseline ECT and an ECT after 4 weeks BDP treatment (100 μg twice daily)

3.2 | (Childhood) asthma control test

At baseline visit, mean (C)-ACT score was 19.0 ± 4.3. Based on their (C)-ACT, 50% of participants could be considered controlled ((C)-ACT score >19), although all participants were uncontrolled based on their ECT result. After 4 weeks of BDP treatment, mean (C)-ACT score significantly improved to 21.7 ± 4.2 ($p = .011$) with 28% of children having an uncontrolled (C)-ACT score. However, there was no significant difference in (C)-ACT score between responders and non-responders (respectively, 22.0 ± 3.9 and 20.2 ± 5.5, $p = .454$).

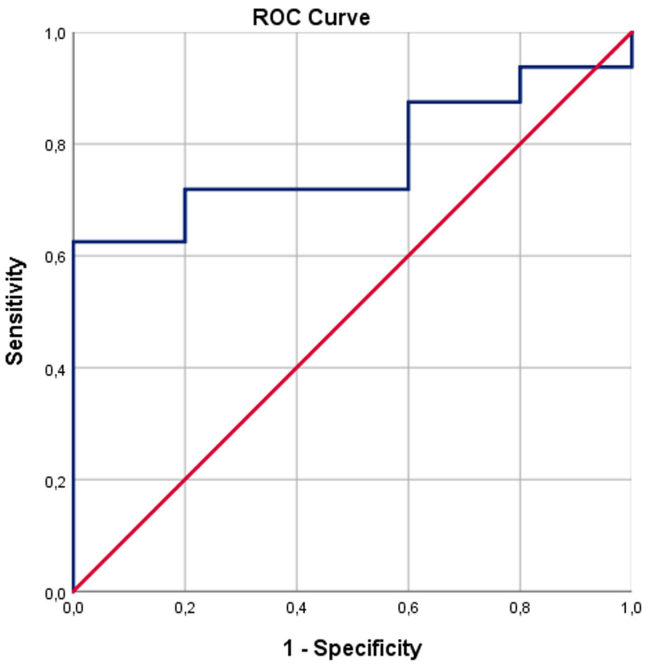

FIGURE 3 Receiver Operating Characteristic Curve for difference in post-exercise FEV1 after a single dose BDP (200 μg) as a predictor for being a responder to BDP after 4 weeks of BDP treatment (100 μg twice daily). A cut-off of ≥8% fall in FEV1 after a single dose BDP shows a specificity of 100% (CI: 55.0%–100%) and a sensitivity of 62.5% (CI: 45.0%–77.9%) for being a responder after 4 weeks of BDP treatment

TABLE 3 Cross-tabulation of responders versus non-responders after 4 weeks of BDP treatment (100 μg twice daily) with cut-off value of >8% reduction in absolute fall in FEV1 after a single dose BDP (200 μg)

Response after single-dose BDP	Response after 4 weeks of BDP treatment		
	Responder[a]	Non-Responder	Total
≥8% fall	20	0	20
<8% fall	12	5	17
Total	32	5	37

Abbreviations: BDP: Beclomethasone-dipropionate; FEV1: Forced Expiratory Volume in 1 s.

[a]A responder is defined as ≥25% relative reduction in post-exercise % fall in FEV1 compared to baseline after respectively a single dose BDP or 4 weeks BDP treatment ($p < .001$).[30,38]

4 | DISCUSSION

The majority of steroid-naïve children and adolescents in our study showed a significant effect of a single inhaled dose of BDP in conjunction with a marked effect against EIB after 4-week treatment. We found a significant relation between the improvement of exercise-induced fall in FEV1 to a single-dose BDP (200 μg) and response after 4 weeks of treatment. An improvement in fall in post-exercise FEV1 of more than 8% after a single-dose BDP compared with baseline could predict BDP efficacy against EIB after 4 weeks of treatment.

This is the first study that investigated the predictive value of the effect of a single inhaled low dose of BDP on the longer-term effect of BDP against EIB. A previous pilot study (2012) showed a significant relation between the change in Mannitol PD_{15} (provoking dose of mannitol to cause a ≥ 15% fall in FEV_1) after a single dose and 4-week treatment with BDP, in line with our results.[39] Two other studies examined the relevance of single-dose effects of asthma medication for long-term efficacy, also using indirect bronchoprovocation tests. Indirect challenges trigger airway narrowing through the activation of inflammatory pathways that result in the endogenous release of mediators, in contrast to direct bronchoprovocation challenge tests (e.g. methacholine and histamine).[35,40,41] Anderson et al. showed the potential relevance of a single-dose effect to assess the capacity to which airway hyperresponsiveness may be reduced.[41] They demonstrated a significant relationship between the reduction in sensitivity to a 4.5 per cent saline aerosol challenge after a single-dose sodium cromoglycate and after 3- to 8-week treatment with budesonide in adults.[41] Kersten et al. found a significant relation between the single dose effect of montelukast and long-term efficacy, facilitating the identification of responders to montelukast.[38] These studies highlight the relevance of a single dose effect for long-term treatment response.[38,39] In our cohort, there was a significant improvement in post-exercise fall in FEV1 after a single-dose BDP compared with baseline that further improved after 4 weeks of treatment. Twelve participants (32%) improved after 4 weeks of treatment with BDP, however, showed less than 8% improvement after a single-dose BDP, and we considered them to be 'late responders'. The different pathophysiological effects of a single-dose ICS and long-term treatment can possibly explain the difference in responsiveness to BDP after a single dose and 4-week treatment in these participants. Acute effects of ICS can be primarily attributed to vasoconstriction and suppression of increased microvascular permeability and plasma leakage into the airway lumen.[42,43] Furthermore, Kippelen et al demonstrated an acute reduction in excretion of mast cell metabolites, the most sensitive markers of mast cell activation, following hyperpnea with dry air after a single high dose of ICS.[28] Other hypotheses for this acute inhibition in mast cell mediator release are that ICS lead to a change in fluid balance of the airway wall and therefore reduce the osmotic stimulus during exercise[28,44] or that ICS inhibit mast cell release of mediators directly through a reduction in intracellular calcium, as has been reported in guinea pigs.[45] Long-term effects of ICS are likely due to the increased synthesis of anti-inflammatory proteins, reduction in inflammatory cells in the airways and inhibition of the chronic remodelling process that is only noticeable after a prolonged period.[42,43,46] Vascular effects could be more variable depending on the actual hyperaemic state of the airway mucosa, especially in mild or moderate EIB. Five participants (14%) did not respond after 4 weeks of treatment, which is in line with previous studies on prevalence of non-responsiveness to ICS.[11,14-21] All non-responders had less than 8% improvement in fall in post-exercise FEV1 after a single-dose BDP. None of them had severe EIB, and there was a lower prevalence of atopy among non-responders. Previous studies also reported a more favourable response of ICS in children and adolescents with more severe asthma and/or high levels of markers associated with allergic inflammation.[42,47,48]

In young children, EIB is strongly associated with asthma.[49,50] As asthmatic children age, the spectrum of symptoms usually changes. Commonly exercise-induced symptoms become more prominent, while other symptoms and the prevalence of exacerbations tend to decline.[51,52] In adults, EIB can occur in the absence of chronic asthma.[53] Although EIB in children and adolescents often is a sign of persistent airway inflammation,[49,53,54] clinicians and patients may be tempted to stop anti-inflammatory maintenance therapy. Since children are physically active on a daily base, this may lead to frequent use of SABA's without ICS and compromise of participation and performance in physical activities with peers. This dilemma was addressed in the GINA guidelines.[1] Perception of severity of EIB is often poor in young asthmatics as shown by the discrepancy between the ACT score and EIB occurrence in this and other studies.[55-58]

A single-dose method could support clinicians to provide patients more personalized and substantiated recommendations to manage their exercise-induced symptoms and to motivate patients to adhere to their anti-inflammatory therapy. The proposed cut-off value of 8% improvement in post-exercise FEV1 after a single-dose BDP to identify good responders for long-term treatment with BDP has to be validated in future studies.

Our data can be affected by several factors. Firstly, in the original study design BDP use was supposed to be monitored by smart inhalers but due to technical problems these were not usable during this study. Self-reported adherence was, therefore, assessed at study visits but could not be objectively verified. Considering the short duration of 4 weeks, it is expected that reported adherence was reliable. Secondly, lack of a placebo arm disallows analysis of differences as a result of variability in response to an ECT. However, an ECT has a good repeatability[59] and all ECTs in this study were performed in a climate chamber under standardized conditions to further minimize climatic confounders.

In conclusion, we found that the response to a single-dose BDP against EIB has a predictive value for term efficacy of BDP after 4 weeks. This could support clinicians to provide substantiated and personalized management of EIB in childhood asthma.

AUTHOR CONTRIBUTION

Vera Sabine Hengeveld: Data curation (equal); Formal analysis (lead); Investigation (equal); Project administration (equal); Writing – original draft (lead); Writing – review & editing (lead). **Natasja Lammers:**

Data curation (equal); Investigation (equal); Project administration (equal); Writing – original draft (supporting); Writing – review & editing (supporting). **Mattienne van der Kamp:** Formal analysis (supporting); Investigation (supporting); Writing – original draft (supporting); Writing – review & editing (supporting). **Job van der Palen:** Formal analysis (supporting); Methodology (equal); Supervision (supporting); Writing – review & editing (supporting). **Bernard J. Thio:** Conceptualization (lead); Methodology (equal); Supervision (lead); Writing – original draft (supporting); Writing – review & editing (supporting).

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Not applicable.

CONFLICT OF INTEREST

All authors state that they have no conflict of interests to declare.

PEER REVIEW

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