Protective Effect of a Low Single Dose Inhaled Steroid Against Exercise Induced Bronchoconstriction

R. Visser, MD,[1]* M. Wind, MD,[2] B. de Graaf, MD,[1] F. H. C. de Jongh,[3] J. van der Palen,[4,5] and B. J. Thio, MD[1]

Summary. Objective: Daily use of inhaled corticosteroids (ICS) reduces exercise induced bronchoconstriction (EIB) in asthmatic children. A high single dose of ICS also provided acute protection against EIB. Objective of this study is to investigate whether a low single dose of ICS offers protection against EIB in asthmatic children. Methods: 31 Mild asthmatic children not currently treated with inhaled corticosteroids, 5–16 years, with EIB (fall in $FEV_{0.5/1} \geq 13\%$) were included in a prospective intervention study. They performed two ECT's within 2 weeks. Four hours before the second test children inhaled 200 μg beclomethasone-dipropionate (BDP) with a breath-actuated inhaler (BAI). Results: The median fall in $FEV_{0.5/1}$ after 200 μg BDP was significantly reduced from 30.9% at baseline to 16.0% ($P < 0.001$). Twenty children (64.5%) showed a good response to 200 μg BDP (≥50% decrease in fall of $FEV_{0.5/1}$), while 8 children showed a moderate response (25–50%), and three children showed no response at all (< 25%). Conclusion: A low single dose ICS offers acute protection against EIB in the majority of asthmatic children not currently treated with inhaled corticosteroids. **Pediatr Pulmonol. 2015;50:1178–1183.**

Key words: Pediatric asthma; exercise induced asthma; protection; inhaled corticosteroids.

Funding source: none reported.

INTRODUCTION

Exercise induced bronchoconstriction (EIB) is defined as a transient narrowing of the airway during or after physical exercise.[1] EIB is a highly prevalent and specific symptom of childhood asthma and reflects airway inflammation.[1,2] Of all asthma symptoms, EIB is considered to be the most detrimental on the quality of life of children.[3,4]

An exercise challenge test (ECT) can detect EIB, diagnose asthma and evaluate asthma treatment.[5] Daily use of inhaled corticosteroids (ICS) reduces exercise induced bronchoconstriction (EIB) in asthmatic children. Thio et al. also showed an acute protective effect of a high single dose of ICS in asthmatic children not currently treated with inhaled corticosteroids.[6] The effect, however, of a low single dose of ICS against EIB is unknown.

The aim of this study was to investigate the protective effect against EIB of 200 μg beclomethasone-dipropionate (BDP) inhaled 4 hr prior to an ECT in asthmatic children not currently treated with inhaled corticosteroids. The secondary aim was to identify individual characteristics of children responding to a single dose ICS.

METHODS

Patients

Children 5–16 years, with a paediatrician diagnosis of mild asthma based on GINA guidelines were recruited from the outpatient clinic of the paediatric department of Medisch Spectrum Twente, Enschede, the Netherlands, from October 2013 through February 2014.[7] All children

[1] Department of Pediatrics, Medisch Spectrum Twente, KA Enschede, The Netherlands.

[2]Department of Emergency, Röpcke-Zweers Hospital, Hardenberg, The Netherlands.

[3]Department of Pulmonary Function, Medisch Spectrum Twente, Enschede, The Netherlands.

[4]Medical School Twente, Medisch Spectrum Twente, Enschede, The Netherlands.

[5]Department of Research Methodology, Measurement and Data Analysis, University of Twente, Enschede, The Netherlands.

Conflict of interest: none

*Correspondence to: Dr. Reina Visser, Department of Pediatrics, Medisch Spectrum Twente, P.O. Box 50 000, 7500 KA Enschede, The Netherlands. E-mail: reinavisser85@gmail.com, r.visser@mst.nl

Received 22 July 2014; Revised 2 October 2014; Accepted 19 October 2014.

DOI 10.1002/ppul.23144
Published online 21 November 2014 in Wiley Online Library (wileyonlinelibrary.com).

had asthmatic symptoms for more than one year. None of the children had used ICS or nasal corticosteroids for at least two months prior to the study. Half of the children had never used ICS before, the other half had stopped ICS based on symptoms. All children performed an ECT to assess for EIB and when EIB was identified, confirming the diagnosis of asthma, children proceeded to the second ECT. Children with other pulmonary or cardiac disorders were excluded. Children being admitted to the hospital or being prescribed systemic corticosteroids because of an exacerbation in the last 2 months prior to the ECT were excluded.

First Exercise Challenge Test

The ECT's were performed as previously described by Van Leeuwen et al. and Driessen et al.[8,9] In summary children 5–10 years old jumped for a maximum of 6 min on a jumping castle in cold, dry air conditions (9.5–10 degrees and humidity 57–59%) in an indoor ice skating rink. Children 12–16 years old performed the ECT on a treadmill with a 10° slope (Trimline® 7150). Children 10–12 years old could choose between the two ECT formats. Heart rate was continuously monitored by a radiographic device (Garmin Forerunner 610) and target was to achieve 80–90% of maximum heart rate. Pulmonary function was measured before, during and after exercise using standard ERS protocol[10] in case of an ECT on the jumping castle and in case of running on the treadmill only before and after the ECT. An exercise induced fall in FEV_1 of $\geq$13% (or $FEV_{0.5}$ if FEV_1 was not reproducible in the youngest children) compared to baseline was considered as positive for EIB.[11] The percentage of predicted baseline $FEV_{0.5/1}$ was measured with the aid of the Koopman formulas.[12]

Second Exercise Challenge Test

Children performed the second ECT according to the aforementioned procedure within two weeks after the baseline ECT. This ECT was preceded by the inhalation of 200 μg BDP (Qvar®) 4 hr prior to the ECT, administered with a breath-actuated inhaler (BAI). In the hours between the medication administration and the ECT the child was not allowed to perform exercise, so parents had to take their child to the ice skating rink by car and older children could arrive by bus or scooter.

The degree of protection of BDP against EIB was assessed for each individual child. Mean protection was defined as ((fall in $FEV_{0.5/1}$ at baseline−fall in $FEV_{0.5/1}$ after BDP)/ fall in $FEV_{0.5/1}$ at baseline).[13] Children with a decrease in fall of $FEV_{0.5/1}$ of $\geq$50% were classified as responders, a decrease of 25–50% was classified as a moderate response and non-responders were children with a decrease of <25% in fall of $FEV_{0.5/1}$.

Questionnaire

Children <12 years old, together with their parents, answered the Childhood Asthma Control Test (C-ACT) at the end of the study to measure asthma control.[14] Children >12 years old answered the Asthma Control Test (ACT).[15]

Sample Size Calculation

This study was part of another study on EIB, which included 32 patients. Given a sample size of 31 patients, a power of 90%, an alpha of 5% and an expected standard deviation in the fall in $FEV_{0.5/1}$ of 15%,[16] the smallest detectable difference in fall in $FEV_{0.5/1}$ between the baseline ECT and the ECT after inhaling BDP was 9.03%.

Statistical Analyses

Best values of spirometric measurements were used for statistical calculations. EIB was defined as an exercise induced fall of $\geq$13% in FEV_1 or $FEV_{0.5}$ compared to baseline value. Results were expressed as mean values $\pm$ standard deviation (SD) for normally distributed data, as median (minimum; maximum) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal.

Within person changes in continuous variables (e.g. fall in FEV_1 or $FEV_{0.5}$) were analysed with a paired T-test or a Wilcoxon signed rank, as appropriate. Between-group differences (responders versus non-responders) in continuous variables (e.g. age) were analysed with a independent T-test or a Mann-Whitney U test, as appropriate. Between-group comparisons of nominal or ordinal variables (e.g. gender) were performed by Chi-square tests. A two-sided value of $P < 0.05$ was considered statistically significant. Data were analyzed with SPSS® for Windows® version 20 (IBM, Chicago, IL) analytical software.

Ethical Considerations

This study was approved by the Medical Ethics Review Board Twente. All children and parents/guardians received written patient information and provided written informed consent to participate in this study.

RESULTS

Of the 96 eligible patients, 62 patients entered the study after informed consent was obtained. Twenty-six did not have EIB. After finishing the study five children were excluded (three children performed unreliable lung function measurements and two had a worsening of their asthma) and so 31 (22 boys, mean age 8.6 years, range 5–16), composed the study group (Fig.1). Twenty-five children (80.6%) performed the ECT's on the jumping

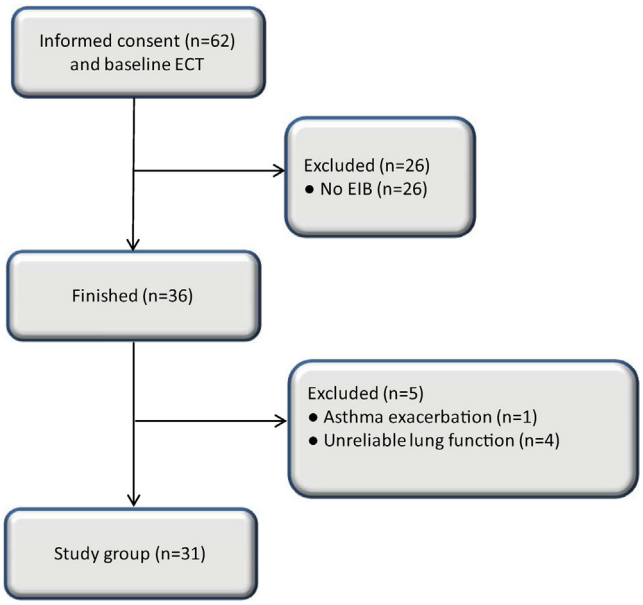

Fig. 1. Flow chart of inclusion.

castle. Mean $FEV_{0.5/1}$ as a percentage of predicted was 81.9% ± 10.2%. 23 Children (74.2%) children had well controlled asthma. Table 1 summarizes all baseline characteristics.

Baseline ECT

All children achieved their target heart rate during the ECT. Mean fall of $FEV_{0.5/1}$ was 35.0% ± 14.5%. 35% of the children were too young to perform reliable FEV_1 measurements, so in that case the $FEV_{0.5}$ was reported.

TABLE 1— Baseline Characteristics of the Study Group

Number of patients	31
Age, years (mean ± SD)	8.6 ± 2.8
Boys (N (%))	22 (71)
Hospitalization before the study (N (%))	13 (41.9)
$FEV_{0.5/1}$ % predicted (mean ± SD)	81.9 ± 10.2
$FEV_{0.5/1}$ fall in % (median, IQR)	30.9 (21.8; 49.5)
Break through asthma (N (%))	15 (48.4)
Exercise test format	
Jumping castle (N (%))	25 (80.6)
Treadmill (N (%))	6 (19.4)
Short acting bronchodilator agent p.r.n. (N (%))	31 (100)
Leukotriene receptor antagonist (N %))	3 (9.7)
Allergy	
Proven (N (%))	21 (67.7)
Unknown (N (%))	10 (32.3)
(C-)ACT ≤ 19 (N (%))	8 (25.8)
(C-)ACT baseline score (mean ± SD)	21.1 ± 3.9

Data are expressed as mean values ± standard deviation, median + interquartile range (IQR) or numbers (percentage); $FEV_{0.5/1}$: forced expiratory volume in 0.5 or 1 s, percentage of predicted based on the reference values of Koopman et al.[13] ; Break through asthma: fall in $FEV_{0.5/1}$ ≥13% during exercise; p.r.n. pro re nata; Allergy: proven by radioallergosorbent test or skin prick test;(C)-ACT = (Childhood)-Asthma Control Test: a score ≤19 indicates uncontrolled asthma.[15,16]

Effects on EIB

After inhalation of 200 μg BDP 14 children (45.2%) showed no EIB anymore. Five children (16.1%) still suffered from breakthrough EIB compared to 15 (48.4%) at baseline ($P = 0.006$).

Children showed a significantly smaller fall of $FEV_{0.5/1}$ after inhaling 200 μg BDP (median fall 16.0% IQR 8.6 ; 24.2%) compared to the baseline ECT (median fall 30.9% IQR 21.8 ; 49.5%, $P = <0.001$). Mean protection of BDP against EIB was 48.9% ± 32.6%. Twenty children (64.5%) showed a good response (≥50% decrease in fall of $FEV_{0.5/1}$) to a low single dose BDP. Eight children (25.8%) showed a moderate response (25–50% decrease in fall of $FEV_{0.5/1}$), while three children (9.7%) showed no response at all (<25% decrease in fall of $FEV_{0.5/1}$). Individual responses to BDP are summarized in Figure 2.

Baseline characteristics of the responder and moderate/non-responder group are shown in Table 2. None of these baseline characteristics differed significantly between the two groups, but the non-responder group showed a trend towards more boys ($P = 0.077$) and a higher amount of children being hospitalized because of asthma before the study ($P = 0.076$).

Test results of the baseline ECT and the ECT after inhaling 200 μg BDP are summarized in Table 3.

Nadir and Recovery of EIB

Of the 17 children still showing EIB after inhaling 200 μg BDP, the maximum fall of $FEV_{0.5/1}$ (nadir) appeared significantly earlier after inhaling BDP (108 sec ± 66) compared to baseline (162 sec ± 90) (difference 54 sec, 95%CI 5.5 ; 93.4, $P = 0.03$).

Also, the recovery time of these 17 children ($FEV_{0.5/1}$ within 5% of baseline) was significantly shorter after inhaling 200 μg BDP compared to baseline (19.7 min ±

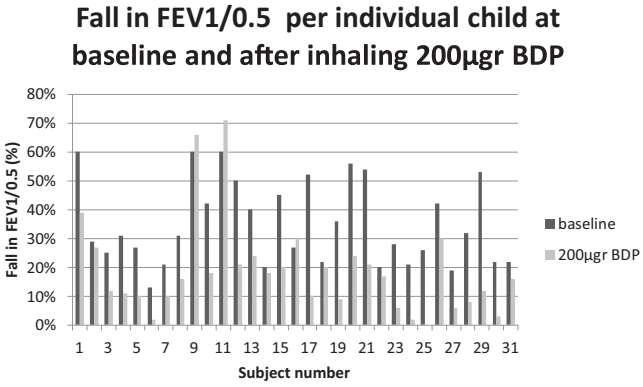

Fig. 2. Individual responses to a low single dose BDP measured in fall in $FEV_{0.5/1}$.

TABLE 2—Characteristics of Responders versus Moderate/non Responders to a Single Low Dose Beclomethasone Dipropionate on Exercise Induced Bronchoconstriction

	Responders	Moderate/non responders	Diff (95%CI); p-value
Number of patients	20	11	
Age, years (mean ± SD)[1]	8.3 ± 3.2	9.2 ± 2.0	0.9 (−1.21; 3.16); $P = 0.370$
Boys (N (%))[2]	12 (60.0)	10 (90.9)	$P = 0.077$
Hospitalisation before the study (N (%))[2]	6 (30.0)	7 (63.6)	$P = 0.076$
$FEV_{0.5/1}$ % predicted (mean ± SD)[1]	82.4 ± 12.0	81.0 ± 5.9	1.4 (−0.08; 0.05); $P = 0.669$
$FEV_{0.5/1}$ fall % (mean ± SD)[1]	34.2 ± 13.5	36.4 ± 16.8	2.2 (−0.09; 0.14); $P = 0.683$
Break through asthma (N (%))[2]	10 (50.0)	5 (45.5)	$P = 0.553$
Exercise test format [2]			
Jumping castle (N (%))	15 (75.0)	10 (90.9)	$P = 0.284$
Treadmill (N (%))	5 (25.0)	1 (9.1)	
Leukotriene receptor antagonist (N (%))[2]	1 (5.0)	2 (18.2)	$P = 0.281$
Allergy [2]			$P = 0.510$
Proven (N (%))	14 (70.0)	7 (63.6)	
Unknown (N (%))	6 (30.0)	4 (36.4)	
(C-) ACT ≤ 19 (N (%))[2]	4 (20.0)	4 (36.4)	$P = 0.281$
(C-) ACT baseline score (median (IQR))[3]	22.5 (20.0–24.0)	22.0 (17.0–23.0)	0.5 $P = 0.670$

Responders: decrease in fall in $FEV_{0.5/1}$ ≥50% compared to baseline. Moderate responders: decrease in fall in $FEV_{0.5/1}$ 25–50% compared to baseline. Non responders: decrease in fall in $FEV_{0.5/1}$ <25% compared to baseline.
$FEV_{0.5/1}$: forced expiratory volume in 0.5 or 1 s, percentage of predicted based on the reference values of Koopman et al.[13] ; Break through asthma: fall in FEV0.5/1 ≥ 13% during exercise. Allergy: proven by blood test or skin prick test; (C)-ACT, (Childhood)-Asthma Control Test: a score ≤19 indicates uncontrolled asthma.[15,16]
[1]Independent T-test.
[2]Chi-square test.
[3]Mann-Whitney U test.

4.5 and 14.9 min ± 6.9, respectively; difference 4.8 min, 95%CI 1.4; 8.1, $P = 0.009$).

DISCUSSION

A low single dose of 200 μg BDP inhaled 4 hr prior to an ECT protected significantly against EIB in asthmatic children not currently treated with inhaled corticosteroids. There was however a considerable variability in the protection against EIB, with a trend towards more boys in the non-responder group.

To our knowledge, this is the first prospective intervention study investigating the acute protective effect of a low single dose of 200 μg BDP 4 hr prior to an ECT on EIB in asthmatic children. Our results correspond to Thio et al. who showed that a single high dose of 1 mg fluticasone 4 hr before an ECT offered an acute protective effect against EIB in asthmatic children.[6] Other studies also showed an acute protection against bronchial hyperresponsiveness (BHR) to indirect stimuli when using high single doses of 1000–1600 μg ICS inhaled 4–8 hr before a challenge in adult asthmatics.[17,18] Kippelen et al. demonstrated that a high single dose of 1500 μg BDP provided significant protection against BHR due to hyperpnea in both untrained adult asthmatics and athletes with EIB.[18]

TABLE 3—Test Results at Baseline and after Inhalation of 200 μgr of Beclomethasone Dipropionate (bdp)

	Baseline	After 200 μgr BDP	Diff (95%CI); *P*-value
$FEV_{0.5}/_1$ % of predicted value (mean ± SD)[1]	81.9 ± 1.2	80.0 ± 12.8	1.9 (−0.02; 0.054); $P = 0.278$
$FEV_{0.5/1}$ fall % (median (IQR))[2]	30.9 (21.8; 49.5)	16.0 (8.6; 24.2)	$P \leq 0.001$
Break through asthma (N (%))[3]	15 (48.4)	5 (16.1)	$P = 0.006$
Nadir in seconds (mean ± SD)[1]	162 ± 90	108 ± 66	54 (5.5; 93.4); $P = 0.030$
Recovery in minutes (mean ± SD)[1]	19.7 ± 4.5	14.9 ± 6.9	4.8 (1.4; 8.1); $P = 0.009$

Data expressed as mean values ± standard deviation, median with interquartile ranges or numbers (percentage). BDP: Beclomethasone Dipropionate. $FEV_{0.5/1}$: forced expiratory volume in 0.5 or 1 s, percentage of predicted based on the reference values of Koopman et al.[13] ; Break through asthma: fall in $FEV_{0.5/1}$ ≥13% during exercise.
[1]Independent T-test.
[2]Mann-Whitney U test.
[3]Chi-square test.

We showed that a low single dose of 200 μg BDP provided ≥50% protection in the majority of children indicating that the effect of 200 μg BDP is already on the flat part of the dose-response curve.

The protective effect of a low single dose ICS against EIB may be clinically profitable for mild asthmatic children who do not require maintenance ICS therapy but with EIB. Bronchoprotection of salbutamol against EIB is, although stronger, short lived and subject to tachyphylaxis.[19–21]

There is no agreement regarding the nature of the exact stimulus that causes EIB. One assumes that exercise induced hyperpnea dries the epithelium, leading to hyperosmolarity of the airway surface fluid. This causes the release of histamine and other inflammatory mediators from mucosal mast cells, resulting in bronchial obstruction.[1,22] The second hypothesis states that exercise-induced hyperventilation results in airway cooling and vasoconstriction. After exercise, when ventilation has normalized, the airways rapidly re-warm leading to vascular engorgement and mucosal edema resulting in bronchial obstruction.[1,23] Since topical steroids have a potent vasoconstrictive effect, the protective effect of a single inhaled dose of BDP against EIB suggests that bronchovascular engorgement and mucosal oedema do play a substantial role in the pathophysiology of EIB. The variability of the response to BDP observed in our study suggests that the relative contribution of vascular engorgement and mucosal edema to airway obstruction may vary from person to person underlining the heterogeneity of asthma in childhood. We were surprised to find a trend towards more boys in the non-responder group which may be due to smaller airways of prepuberal boys compared to girls.[24]

The main strengths of our study include the homogenous group of 31 asthmatic children not currently treated with inhaled corticosteroids. All ECT's were performed in the same setting by the same investigator. Also, a short time period between the two interventions was pursued (<2 weeks) and all tests were carried out by the same investigator in standardized air conditions. Medication administration was supervised by the same investigator in all children.

Limitations of our study are the absence of a placebo group and the fact that the investigator was not blinded to the use of BDP prior to the ECT. The $FEV_{0.5/1}$ as a % of predicted value, prior to the ECT, did not differ between the two ECT's. The reason for this design is explained by the fact that this analysis was part of a more extensive study that analysed the influence of body posture during inhaling BDP prior to an ECT on EIB. In eight children we found severe EIB (fall in $FEV_{0.5/1}$ ≥50%) which is not compatible with mild asthma and does reflect marked airway inflammation. These children were started on maintenance ICS after the study. Severity of EIB as measured with fall in FEV_1 does not correlate well with symptoms as measured with the ACT questionnaire.[25]

The acute response of a single dose ICS in asthmatic children we observed may have implications for guidelines relating to medication restrictions before bronchoprovocative tests. Further dose response studies including different time points after single dosing ICS in asthmatic children with or without maintenance ICS could provide data about the sustained effect of a single dose ICS. Further studies could also investigate if asthmatic children with EIB, without other symptoms of asthma, could profit from the acute effect of a low single dose ICS in the morning.

In conclusion, a low single dose of 200 μg BDP inhaled 4 hr prior to an ECT offered acute protection against EIB in the majority of asthmatic children not currently treated with inhaled corticosteroids.

ACKNOWLEDGEMENTS

We thank Jennie von Doellen for revising the text.

REFERENCES

1. Randolph C. Pediatric exercise-induced bronchoconstriction: contemporary developments in epidemiology, pathogenesis, presentation, diagnosis, and therapy. Curr Allergy Asthma Rep 2013;13: 662–671.
2. Anderson SD. Exercise-induced asthma in children: a marker of airway inflammation. Med J Aust 2002;177 Suppl: S61–S63.
3. Croft D, Lloyd B. Asthma spoils sport for too many children. The Practitioner. 1989; 233:969–971.
4. Merikallio VJ, Mustalahti K, Remes ST, Valovirta EJ, Kaila M. Comparison of quality of life between asthmatic and healthy school children. Pediatr Allergy Immunol 2005;16: 332–340.
5. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000;161:309–329.
6. Thio BJ, Slingerland GL, Nagelkerke AF, Roord JJ, Mulder PG, Dankert-Roelse JE. Effects of single-dose fluticasone on exercise-induced asthma in asthmatic children: a pilot study. Pediatr Pulmonol 2001;32: 115–121.
7. Masoli M, Fabian D, Holt S, Beasley R. Global Initiative for Asthma P. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59: 469–478.
8. van Leeuwen JC, Driessen JM, de Jongh FH, Anderson SD, Thio BJ. Measuring breakthrough exercise-induced bronchoconstriction in young asthmatic children using a jumping castle. J Allergy Clin Immunol 2013;131:1427–1429. e5.
9. Driessen JM, van der Palen J, van Aalderen WM, de Jongh FH, Thio BJ. Inspiratory airflow limitation after exercise challenge in cold air in asthmatic children. Respir Med 2012;106 1362–1368.
10. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crape R, Enright P, van der Grinten CPM, Gustafsson P, et al. Standardisation of spirometry. Euro Respir J 2005;26: 319–338.

11. Vilozni D, Bentur L, Efrati O, Barak A, Szeinberg A, Shoseyov D, et al. Exercise challenge test in 3- to 6-year-old asthmatic children. Chest 2007;132:497–503.
12. Koopman M, Zanen P, Kruitwagen CL, van der Ent CK, Arets HG. Reference values for paediatric pulmonary function testing: The Utrecht dataset. Respir Med 2011;105:15–23.
13. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Euro Respir J 2005;26:153–161.
14. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007;119: 817–825.
15. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113: 59–65.
16. Driessen JM, Nieland H, van der Palen JA, van Aalderen WM, Thio BJ, de Jongh FH. Effects of a single dose inhaled corticosteroid on the dynamics of airway obstruction after exercise. Pediatr Pulmonol 2011;46:849–856.
17. Gibson PG, Saltos N, Fakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: A randomized controlled trial. Am. J. Respir. Crit. Care Med. 2001;163:32–36.
18. Kippelen P, Larsson J, Anderson SD, Brannan JD, Delin I, Dahlen B, Dahlen SE. Acute effects of beclomethasone on hyperpnea-induced bronchoconstriction. Med Sci Sports Exerc 2010;42: 273–280.
19. Stewart SL, Martin AL, Davis BE, Cockcroft DW. Salbutamol tolerance to bronchoprotection: course of onset. Ann Allergy Asthma Immunol 2012;109:454–457.
20. Anderson SD, Caillaud C, Brannan JD. Beta2-agonists and exercise-induced asthma. Clin Rev Allergy Immunol 2006;31: 163–180.
21. Shapiro GS, Yegen U, Xiang J, Kottakis J, Della Cioppa G. A randomized, double-blind, single-dose, crossover clinical trial of the onset and duration of protection from exercise-induced bronchoconstriction by formoterol and albuterol. Clin. Ther. 2002;24:2077–2087.
22. Anderson SD. The prevention of exercise-induced bronchoconstriction: what are the options? Expert Rev Respir Med 2012;6: 355–357.
23. Anderson SD. Exercise-induced bronchoconstriction in the 21st century. J Am Osteopath Assoc 2011;111(11 Suppl 7):S3–10.
24. Seo JH, Hwang SH, Kang JM, Kim CS, Joo YH. Age-related changes of the larynx and trachea assessed by three-dimensional computed tomography in children: Application to endotracheal intubation and bronchoscopy. Clin. Anat. 2014;27:360–364.
25. Madhuban AA, Driessen JM, Brusse-Keizer MG, van Aalderen WM, de Jongh FH, Thio BJ. Association of the asthma control questionnaire with exercise-induced bronchoconstriction. J Asthma 2011;48:275–278.