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The effect of body posture during medication inhalation on exercise induced bronchoconstriction in asthmatic children☆

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ABSTRACT

Rationale: Inhaling medication in a standard body posture leads to impaction of particles in the sharp angle of the upper airway. Stretching the upper airway by extending the neck in a forward leaning body posture may improve pulmonary deposition. A single dose of inhaled corticosteroids (ICS) offers acute, but moderate protection against exercise induced bronchoconstriction (EIB). This study investigated whether inhaling a single dose of ICS in a forward leaning posture improves this protection against EIB.
Methods: 32 Asthmatic children, 5–16 years, with EIB (Median fall in FEV_1 or $FEV_{0.5}$ 30.9%) performed two exercise challenge tests (ECT's) with spirometry in a single blinded cross-over trial design. Children inhaled a single dose of 200 μg beclomethasone dipropionate (BDP) 4 h before the ECT, once in the standard posture and once with the neck extended in a forward leaning posture. Spirometry was also performed before the inhalation of the single dose of BDP.
Results: Inhalation of BDP in both body postures provided similar protection against EIB (fall in FEV_1 or $FEV_{0.1}$ in standard posture 16.7%; in forward leaning posture 15.1%, $p = 0.83$). Inhaling ICS in a forward leaning posture significantly delayed EIB compared to inhaling in the standard posture (respectively 2.5 min ± 1.0 min vs. 1.6 min ± 0.8 min; difference 0.9 min (95CI 0.25; 1.44 min); $p = 0.01$).
Conclusion: Inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in asthmatic children, but the forward leaning posture resulted in a delay of EIB.
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1. Introduction

In recent years there is a trend towards the use of breath-actuated inhalers (BAI's) to overcome coordination problems. A drawback however is the massive impaction in the oropharynx. A radio-labelled study showed that under optimal conditions in children of 5–14 years 40–60% of the dose of beclomethasone dipropionate (BDP) inhaled via a breath actuated inhaler (BAI) impacted in the oropharynx. Oropharyngeal deposition was inversely related to age [1]. Dubus et al. showed that approximately 60% of asthmatic children using inhaled BDP or budesonide reported local side effects such as coughing, hoarseness, dysphonia and oral candidiasis [2].

A recent study of Brandao et al. showed that inhaling nebulised bronchodilators in a forward leaning posture during an asthma exacerbation improved recovery of lung function in asthmatic adults compared to the conventional posture [3]. It was suggested

Abbreviations: ICS, Inhalation corticosteroids; EIB, exercise induced bronchoconstriction; FEV_1, forced expiratory volume in 1sec; $FEV_{0.5}$, forced expiratory volume in 0.5sc; ECT, exercise challenge test; BPD, beclomethasone-dipropionate; BAI, breath actuated inhaler; (C)-ACT, (childhood) asthma control test.

☆ This study was performed in Medisch Spectrum Twente, Enschede, the Netherlands.

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that this was due to an increased pulmonary deposition [4,4a,4b].

Exercise induced bronchoconstriction (EIB) is a highly prevalent and specific symptom of childhood asthma and reflects airway inflammation [5]. Long term regular use of inhaled corticosteroids (ICS) reduces EIB in asthmatic children [6]. Several studies showed that a single high dose of ICS (1000–1600 μg), also offers acute protection against EIB [7–10]. We hypothesize that a single low dose of 200 μg ICS inhaled in a forward leaning body posture with the neck extended would also improve protection against EIB.

The aim of this study was to investigate the protective effect against EIB of a single low dose of 200 μg BDP inhaled 4 h prior to an ECT.

2. Methods

2.1. Subjects

This study had a prospective cross-over design. Children 5–16 years, with a paediatrician's diagnosis of asthma were recruited from the outpatient clinic of the paediatric department of Medisch Spectrum Twente, Enschede, The Netherlands, from October 2013 through February 2014. None were taking ICS or nasal corticosteroids for at least 2 months prior to the study. 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 eight weeks prior to the ECT were excluded.

2.2. Inhalation technique

Children performed two ECT's within a time period of two weeks preceded by the inhalation of 200 μg BDP with an Autohaler® (Qvar®) without a spacer. Four hours prior to one ECT they inhaled BDP in the standard body posture and head position according to the standardized instructions from the Dutch Lung Foundation [11]. Four hours prior to the other ECT they inhaled BDP in the forward leaning body posture with the neck extended (Fig. 1). The different body postures during inhalation were randomized. The investigator performing the ECT was blinded to the body posture in which the children had inhaled their medication.

A well-trained medical student administered the medication at the child's home or school, after a baseline pulmonary function measurement was performed.

2.3. Exercise challenge test

In the hours between the medication administration and the ECT, children were allowed to go to school or play but without exercising. Therefore, parents had to take their child to the ECT by car, while older children arrived by bus or scooter. The two ECT's were performed within a time period of 2 weeks at an indoor ice skating rink, because of the standardized cold and dry air conditions (9.5–10° and humidity 57–59%), reflecting real life outdoor conditions in the Netherlands. The minimal time period between the two ECT's was 48 h.

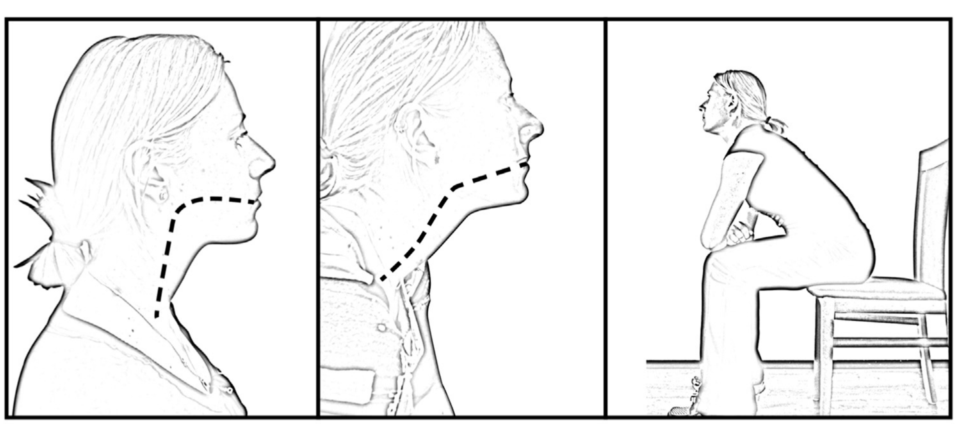
The ECT's were performed as previously described by Van Leeuwen et al. and Driessen et al. [12,13]. In summary, children 6–10 years old jumped for a maximum of 6 min on a jumping castle and children 12–16 years old performed both ECT's on a treadmill with a 10° slope (Trimline® 7150). Children 10–12 years old could choose between the two ECT formats. Heart rate was continuously monitored by a radiographic device (Garmin Forerunner 610) and the target was to achieve 80%–90% of the maximum estimated heart rate (220-age). Pulmonary function was measured before, during and after exercise using standard European Respiratory Society (ERS) protocol [14] in case of an ECT on the jumping castle and only before and after the ECT in case of running on the treadmill. An exercise induced fall in FEV_1 of ≥13% (or $FEV_{0.5}$ if FEV_1 was not reproducible in the youngest children) compared to baseline was considered as positive for EIB [15]. An exercise induced fall in FEV_1 or $FEV_{0.5}$ ≥13% during exercise compared to baseline was considered positive for break through asthma. Percentage of predicted baseline FEV_1 was measured with the aid of the Koopman formulae [16].

2.4. Questionnaires

Children <12 years old answered, with their parents, the Childhood Asthma Control Test (C-ACT) at the end of the study to measure asthma control. Children ≥12 years old answered the Asthma Control Test (ACT) [17,18].

Children (and parents) were asked for the body posture and head position they commonly used during inhaling medication at home.

Children were also asked for any possible discomfort during the forward leaning posture.



Curved airway in standard body posture | Stretched airway in forward leaning body posture | Forward leaning body posture

Fig. 1. Different body postures during BDP inhalation.

2.5. Sample size calculation

A previous study with a comparable design showed an average fall in FEV_1 of 30% (SD ± 15%) after the exercise challenge test in the placebo group [19]. The intervention group received a high dose inhaled corticosteroid (1000 μg fluticasone propionate) with the standard posture before the ECT and showed an average fall in FEV_1 of 20% (SD ± 15%).

Reviewing the literature about the acute effects of a single dose ICS we concluded that a range of high doses all had a comparable effect which implies these doses are on the flat part of the dose response curve. We chose a low dose to be on the steep part of the dose response curve in order to maximise the contrast between inhaling in the different body postures. Also we adjusted the choice of our dose of BDP to the better deposition of BDP compared to fluticasone propionate. We hypothesized that inhalation of 200 μg BDP with the standard posture before an exercise challenge test would not protect against EIB and would be comparable to the placebo group of Driessen et al. [19]. We hypothesized inhalation of 200 μg BDP with the forward leaning posture would have the same protective effect against EIB compared to a high dose inhaled steroid used in the study of Driessen et al. A sample size of 32 achieves 81% power to detect a difference of 7.5% in fall in FEV_1 between the null hypothesis mean of 30.0% and the alternative hypothesis mean of 22.5% with a known standard deviation of 15.0% and with a significance (alpha) of 0,05 using a two-sided one-sample t-test.

To take possible drop outs into account we aimed to include 38 children.

2.6. Statistical analyses

Best values of spirometric measurements were used for statistical calculations. EIB was defined as an exercise induced fall of ≥13% in FEV_1 or $FEV_{0.5}$ compared to baseline value. Results were expressed as mean values ± 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 $_{FEV0,5/1}$) were analysed with a paired T-test or a Wilcoxon signed rank, as appropriate. Between-group comparisons of nominal or ordinal variables were performed by Chi-square tests. For the analysis of correlated proportions a McNemar test was used. To assess the correlation between two continuous variables Pearson's correlation coefficient was computed. A possible period effect was analysed with the Hills and Armitage test. A two-sided value of $P < 0.05$ was considered statistically significant. Data was analysed with SPSS® for Windows® version 21 (IBM, Chicago, IL, USA) analytical software.

2.7. Ethical considerations

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

3. Results

Of the 95 eligible subjects, 22 declined to participate; the majority for logistical reasons.

32 Children (23 boys, mean age 8.8 years, range 5–16) composed the study group (Fig. 2).

No period effects or carry over effects were observed in this study (all p values > 0.33).

25 Children (78.1%) performed the ECT's on the jumping castle. Mean FEV_1 or $FEV_{0.5}$ as a percentage of predicted (FEV_1 or $FEV_{0.5}$%predicted) was 81.3% ± 10.5%. 23 Children (71.9%) had well controlled asthma. Table 1 summarizes all baseline characteristics.

Baseline mean FEV_1 or $FEV_{0.5}$% predicted did not differ significantly between both ECT's (standard posture 78.7% ± 14.7%, forward leaning posture 76.0% ± 13.4% (difference 2.7% (95CI 1.7; 7.1%); p = 0.22). Inhaling ICS in a forward leaning posture provided significantly more bronchodilatation compared to inhaling in the standard posture (respectively 5% ± 9.4% vs. 1.1% ± 7.8%; difference 3.9% (95CI 0.2; 7.6%); p = 0.04). Fig. 3 shows the bronchodilatation in both body postures before and after administration of 200 μg.

Median fall in FEV_1 or $FEV_{0.5}$ did not differ significantly between the standard posture and forward leaning posture (respectively 16.7% (IQR 9.0%; 24.2%) and 15.1% (IQR 9.9%; 26.9%), difference 1.6%, p = 0.83).

The number of children showing EIB after administration of 200 μg BDP in the standard posture (18 children, 56.3%) did not differ from the forward leaning posture (19 children, 59.4%).

The protection of 200 μg inhaled BDP in the forward leaning posture on EIB was not correlated to the bronchodilating effect of 200 μg inhaled BDP as described above (p = 0.33, r = 0.179).

The time to maximum fall in FEV_1 (nadir) in the forward leaning posture was significantly later compared to the standard posture (respectively 2.5 min ± 1.0 min vs. 1.6 min ± 0.8 min; difference 0.9 min (95CI 0.25; 1.44 min); p = 0.01).

Table 2 shows the differences in nadir and recovery time between the two body postures.

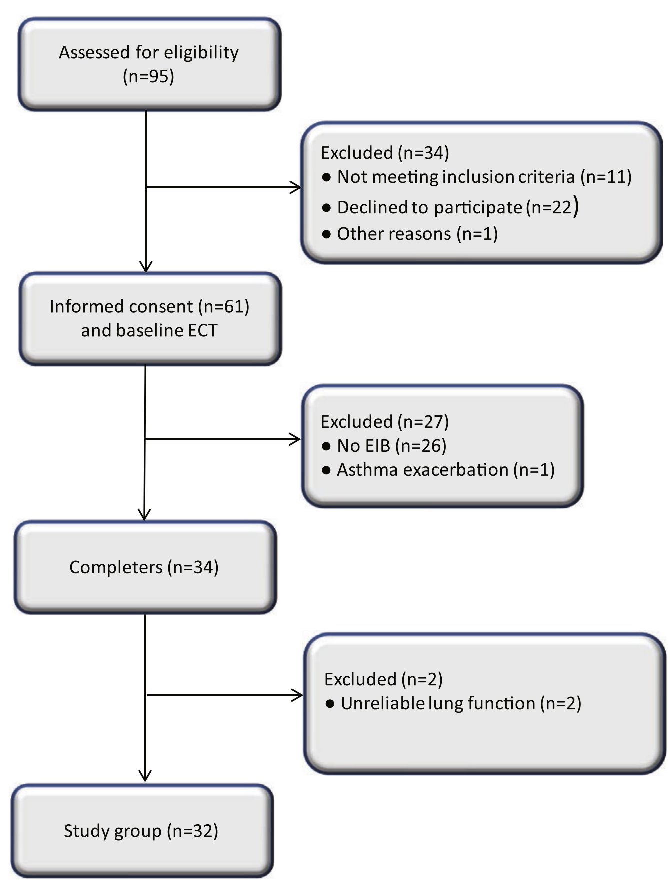


Fig. 2. Flow chart of inclusion.

Table 1
Baseline characteristics of study group.

Number of patients	32
Age, years (mean, SD)	8.8 ± 2.9
Boys (N, %)	23 (71.9)
$FEV_{0.5/1}$%predicted (mean, SD)	81.3 ± 10.5
$FEV_{0.5/1}$ fall (mean, SD)	35.0 ± 14.3
Hospitalisation before the study (N, %)	14 (23.8)
Jumping castle (N, %)	25 (78.1)
Leukotriene receptor antagonist (N, %)	4 (12.5)
Allergy (N, %)	22 (68.8)
Proven	10 (31.3)
Unknown	
(C)-ACT baseline score (mean, SD)	20.9 ± 4.0
(C)-ACT ≤ 19 (N, %)	9 (28.1)

$FEV_{1\ or\ 0.5}$: forced expiratory volume in 1 or 0.5 s, percentage of predicted based on the reference values of Koopman et al. [16]; Allergy: proven by radioallergosorbent test or skin prick test; (C)-ACT = (Childhood)–Asthma Control Test: a score ≤19 indicates uncontrolled asthma [17,18].

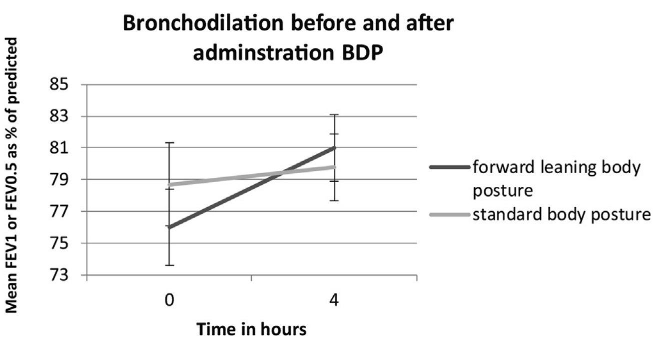


Fig. 3. Bronchodilation in both body postures before and after administration of 200 μg BDP.

3.1. *Questionnaires*

In the home situation nearly all children inhaled in the sitting or standing upright position with the head horizontal. One child received medication while he was lying, and one child pushed her head in anteflexion. One child could not answer the questionnaire because he did not use medication at home. Twenty three children experienced no bodily discomfort in the forward leaning posture. The other nine experienced a little discomfort, especially in the neck and back.

4. Discussion

Inhalation of a single dose BDP in both the forward leaning posture and the standard posture had similar efficacy against EIB in asthmatic children.

To our knowledge, this is the first prospective intervention study investigating the protective effect of a low single dose of BDP inhaled in different body postures on EIB in steroid naïve asthmatic children. Recently, BAI's gained popularity as they are child friendly and easy to handle. A drawback however is the massive impaction in the oropharynx. Previously, we and others showed that a high single dose of ICS reduced EIB [7–10]. We speculated that inhaling a low dose of ICS in a forward leaning posture, but not in the standard posture, would also provide protection against EIB. However, we found a similar efficacy against EIB in both body postures. The magnitude of the effect was similar compared to previous studies with a high single dose of ICS. The protective effect against EIB of a low dose BDP inhaled in the standard posture is recently published by our study group [20].

Table 2
Nadir and recovery time in the standard and forward leaning body posture.

	Standard body posture	Forward leaning body posture	Difference	P-value (95CI)
Nadir	97 s ± 46	148 s ± 58	51 s	P = 0.01 (15.0; 86.6)
Recovery	15.5 min ± 6.8	15.9 min ± 6.1	0.4 min	P = 0.79 (−2.64; 3,41)

Data expressed as mean ± SD. Nadir: time after exercise to maximum fall in FEV_1 or $FEV_{0.5}$ (time in seconds). Recovery: time after exercise of recovery of FEV_1 or $FEV_{0.5}$ within 5% of baseline (time in minutes).

The protective effect of a single dose of ICS in asthmatic children on EIB is probably mediated by the acute vasoconstrictive effect of ICS on the hypertrophied and reactive hyperplastic capillary bed of inflamed airways of asthmatics. Kippelen et al. showed that a single dose of beclomethasone also blocked the release of mast cell mediators, such as PGD2, leading to airway narrowing [8].

We observed a small, clinically non relevant, but significantly stronger bronchodilating effect of inhaling 200 μg BDP in the forward leaning posture compared to inhaling in the standard posture. Previous studies found a similar acute bronchodilating effect, but with a high single dose of ICS in a standard posture in steroid naïve asthmatic children and adults (1000–1600 μg) [21–24].

Children's EIB differs from adult's EIB. The time after exercise to maximal fall of FEV_1 is relatively short [13]. A small minority of children show also break-through exercise induced asthma, i.e. a decline in lung function of ≥13% during exercise [13]. This may lead to dropping out of exercise during play and sports. Resuming of exercise before the maximum fall in FEV_1 reopens the airways and may preclude children from dropping out [25]. So, inhaling a single dose of BDP in the forward leaning posture which significantly delayed the fall in FEV_1 from 1.6 min to 2.5 min after exercise is clinically profitable for children. Apparently, the forward leading posture during inhalation of ICS reinforced bronchodilatory influences during exercise possibly by a higher pulmonary deposition of ICS.

Dubus et al. showed that 60% of asthmatic children using inhaled BDP or budesonide reported local side effects such as coughing, hoarseness, dysphonia and oral candidiasis [2]. A forward leaning posture leading to less impaction of inhaled medication in the upper airway could reduce side effects.

Brandao et al. showed a faster recovery of lung function after inhaling nebulised bronchodilators in a forward leaning posture during an asthma exacerbation in asthmatic adults compared to inhaling in a standard posture [3]. Indeed Listro et al. showed a trend towards less airway resistance when the head was extended in a small study of healthy adults [26]. Nebulising in a forward leaning posture implicates breathing in this posture, whereas our children only inhaled in the forward leaning posture. A sustained period of time breathing may have influenced pulmonary mechanics as well, resulting in a faster recovery of lung function.

The main strengths of our study include the homogenous group of steroid naïve asthmatic children. Additionally, the same investigator performed all ECT's within a period of 2 weeks in a standardised cold air condition reflecting the mean outdoor condition in The Netherlands. This investigator was blinded to the body posture in which the children had inhaled their medication. Limitations of our study are the selection of steroid naïve asthmatic children, and the study design which precludes blinding of the children regarding body posture.

A future study should investigate the effect of inhaling a lower dose of BDP (100 μg) in a forward leaning posture on EIB, aiming to be on the steep part of the dose response curve.

5. Conclusions

In conclusion, inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in asthmatic children. The forward leaning posture resulted in postponed EIB compared to the standard posture which is clinically profitable for children during play and sports. This suggests that body posture during inhalation can influence effects of inhaled medication, probably by a change in pulmonary deposition.

Error bars represent Standard Error. Standard posture: $p = 0.420$ (95CI −0.039; 0.017). Forward leaning posture: $p = 0.005$ (95CI −0.084; −0.017). Improvement FEV_1 or $FEV_{0.5}$ as % of predicted was significantly higher in the forward leaning posture: $p = 0.041$ (95CI −0.076; −0.002).

BDP: beclomethasone dipropionate.

Conflicts of interest statement

Reina Visser (MD): conflicts of interest: none.
Mariet Wind (MD): conflicts of interest: none.
Beike J. de Graaf (MD): conflicts of interest: none.
Frans.H.C. de Jongh (PhD): conflicts of interest: none.
Job van der Palen (MSc, PhD): conflicts of interest: none.
Bernard.J.Thio (PhD, MD): conflicts of interest: none.

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