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Treatment of exercise-induced asthma with beclomethasone dipropionate in children with asthma

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Treatment of exercise-induced asthma with beclomethasone dipropionate in children with asthma. R. Petersen, L. Agertoft, S. Pedersen. ©ERS Journals Ltd 2004.

ABSTRACT: A new hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP) aerosol markedly increases drug delivery to the airways. Therefore, even low doses of HFA-BDP should be effective, and the present study assesses this.

A randomised, double-blind, crossover study was used to compare the effect of placebo, HFA-BDP 50 μg or 100 μg given *q.d.* (QVAR™ Autohaler™; 3M Pharmaceuticals, St. Paul, MN, USA) on exercise-induced bronchoconstriction and exhaled nitric oxide (eNO). After a 14-day run-in, 25 children (5–14 yrs old) entered three 4-week treatment periods, separated by a 1-week washout. After each period, the fall in forced expiratory volume in one second (FEV_1), after an exercise test, and eNO were measured.

Significant treatment effects with no carry-over or period effects were seen for both eNO and maximum fall in FEV_1 after exercise. Differences were seen between placebo (fall in FEV_1=27.9%; eNO=14.4 parts per billion (ppb)) and either dose of HFA-BDP, but not between the two active doses (50 μg: fall in FEV_1=20.8%, eNO=9.3 ppb; 100 μg: fall in FEV_1=20.9%, eNO=8.9 ppb).

In conclusion, low *q.d.* doses of hydrofluoroalkane-beclomethasone dipropionate reduced exhaled nitric oxide and exercise-induced bronchoconstriction. Further studies are needed to assess whether *q.d.* administration of beclomethasone dipropionate is as effective as *b.i.d.* administration.

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Exercise-induced asthma is a common reflection of airway hyperresponsiveness in children with asthma. It may lead to quite marked impairment in everyday physical activities, even in children with mild asthma. International asthma management guidelines often recommend inhaled short-acting β-agonist therapy (as required) for this condition, since inhaled bronchodilators taken immediately prior to exercise effectively prevent the exercise-induced bronchoconstriction. However, this treatment does not influence the underlying airway hyperresponsiveness. Furthermore, children often do not know when they are going to exercise and, therefore, forget their medication, which is taken as needed.

Continuous treatment with inhaled corticosteroids (ICS) also offers good protection against exercise-induced bronchoconstriction [1–9]. In contrast to inhaled bronchodilators, ICS do not have to be taken immediately prior to the exercise, and they modify airway hyperresponsiveness. The clinically effective dose for exercise-induced asthma may be different from the dose required to control other asthma outcomes [1, 5, 9–12], and the shape of the dose-response curve for exercise-induced bronchoconstriction may also be different from that of other asthma outcomes. Therefore, more information is needed about the dose-response relationships of the protection of various ICS against exercise-induced bronchoconstriction, in order to ensure optimum therapy with ICS against this condition and to establish what doses of ICS are needed to decrease the bronchial responsiveness so that exercise-induced bronchoconstriction can be adequately controlled.

A new formulation of hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP; QVAR™; 3M Pharmaceuticals, St. Paul, MN, USA) produces an extra-fine aerosol spray that, compared with conventional inhalers, increases the amount of drug delivered to the lungs [13–20]. Since more drug per puff is delivered to the site of the disease, it seems reasonable to assume that even very low doses of HFA-BDP will provide a significant therapeutic response. The present dose-response study was designed to assess the effect of low doses (50 or 100 μg *q.d.*) of HFA-BDP extra-fine aerosol on exhaled nitric oxide (eNO) and the protection of exercise-induced bronchoconstriction in children with exercise-induced asthma.

Methods

Patients and methods

Children aged 6–15 yrs with a history of exercise-induced bronchoconstriction were recruited from the current authors' outpatient asthma clinic (Dept of Paediatrics, Kolding Hospital, Kolding, Denmark). In order to be included in the study, the patients had to have a resting forced expiratory volume in one second (FEV_1) of $\geqslant$70% of predicted normal [21], and a documented decrease in FEV_1 of $\geqslant$15% after a standard exercise challenge test at a screening visit.

The study was approved by the regional ethics committee.

Each child gave informed oral assent, and the child's parent or legal guardian gave written informed consent in accordance with the current version of the Declaration of Helsinki.

Patients who were found eligible at the screening visit entered a 2-week run-in period, during which no regular asthma medication was allowed. At the end of this period, each patient returned to the clinic for measurement of eNO, followed by an exercise challenge test. At the end of the run-in, patients who also demonstrated a maximum fall of $\geqslant$15% in FEV1 post-exercise entered the trial, which was a randomised, double-blind, placebo-controlled, single-centre crossover study, consisting of three 4-week study periods, each separated by a 1-week washout. The following treatments were given during the double-blind periods: HFA-BDP 50 μg, HFA-BDP 100 μg, and placebo. Treatments were administered *q.d.* (at approximately the same time each evening) from a breath-actuated device (Autohaler^{TM}; 3M Pharmaceuticals). Patients were trained in the correct use of the Autohaler before they entered the study. Compliance was assessed using the weights of the canisters. The predicted weights and weights after actual use were compared.

Throughout the study, each patient continued to use a short-acting β-agonist as needed to treat asthma symptoms; no other asthma medication was allowed. Measurements of eNO and an exercise challenge test were performed at the end of each treatment period. Diary card recordings of peak expiratory flow (PEF), asthma symptoms and sleep disturbance scores, and inhaled short-acting β-agonist use were undertaken throughout the study.

Exercise challenge test

Each patient exercised on a treadmill with a slope of 12%. The speed was adjusted so that the patient's heart rate reached or exceeded 180 beats·min^{-1} during the last 5 min of exercise. During the exercise challenge test, the patient wore a nose-clip and inhaled cold (-5°C) dry air through a face mask. The maximum duration of the exercise challenge test was 8 min. Post-exercise spirometry was performed at 2, 4, 6, 10, 15 and 20 min after completion.

Measurement of exhaled nitric oxide

Measurement of eNO was performed at the end of the run-in (start of period 1), and at the end of periods 1, 2 and 3. The measurements were performed using a chemiluminescence analyser, following the method described by KHARITONOV *et al.* [22]. After a full inhalation, the patient exhaled slowly through a mouthpiece (exhalation flow rate: 200 mL·s^{-1}) that bypassed the analyser. The mouthpiece had moderate resistance to ensure that the soft palate was lifted up and partially closed the nasopharynx. The eNO was sampled from a sidearm attached to the mouthpiece. Patients did not use a nose-clip during this procedure. The eNO value was automatically calculated from the chosen part of the curve for the last 10 s, corresponding to the plateau of the exhaled end level. The mean of three measurements was calculated. The analyser was calibrated and the eNO concentration of the ambient air was measured on each study day.

Statistics

The analysis population consisted of all patients who had evaluations performed for at least two treatment periods (thus allowing at least one pairwise treatment difference to be estimable for that patient). For each exercise challenge, the maximal percentage fall in FEV1 (L) following exercise was calculated as:

$$((\text{FEV1 before exercise} - \text{minimum FEV1 following exercise})/\text{FEV1 before exercise}) \times 100\% \quad (1)$$

The maximal percentage fall in FEV1 in each period was compared using an ANOVA with sequence, patient within sequence, treatment, and period as factors in the model. If the treatment effect was statistically significant at $p<0.05$, multiple comparisons were done using Tukey's method. A 95% confidence interval (CI) was calculated for each pairwise difference in the means. The percentage fall from pre-exercise at each time point (t) was calculated as:

$$((\text{FEV1 before exercise} - \text{FEV1 at time t})/\text{FEV1 before exercise}) \times 100\% \quad (2)$$

The mean percentage fall in FEV1 was plotted against time for each treatment. The area under the curve (AUC) for the percentage fall in FEV1 from exercise over the 20-min period was calculated using a trapezoidal rule. The AUC was analysed using the same methods as the primary response.

Pre-exercise pulmonary function tests

The percentage change from baseline in pre-exercise FEV1 at the end of each period was calculated as:

$$((\text{Pre-exercise FEV1 at end of period} - \text{pre-exercise FEV1 at run-in})/\text{pre-exercise FEV1 at run-in}) \times 100\% \quad (3)$$

The treatments were compared using the same ANOVA model as the primary response.

Exhaled nitric oxide levels

The eNO levels were compared at the end of each period using the same methods as the primary response.

Sample size

A sample size of 24 compliant patients completing all three periods was determined, based upon an estimate of the within-patient standard deviation (SD) of 9.5% for the maximal change from baseline in FEV1 following exercise in paediatrics [23]. Given this estimate, a sample size of 24 patients in a crossover design would provide $\geqslant$80% power for detecting a difference in at least one of the treatments of 8% at the α=0.05 level.

Results

A total of 68 patients (ages 6–15 yrs, 22 females and 46 males) were screened with lung function, exercise test and eNO measurement. In total, 20 males and seven females were included in the study. Failure to meet the entry criterion of a fall of $\geqslant$15% in FEV1 post-exercise was the most common reason for noninclusion (37 out of 41). A total of 25 patients completed all three periods. Two patients were discontinued in period 1; the first (placebo) because of an asthma exacerbation and the second because of a toe fracture. The mean age was 10.6 yrs (range 6.0–14.0 yrs) and mean FEV1 % predicted was 87.2% (range 66–116%).

Compliance was assessed by weighing canisters. Mean±SD compliance with the medication was >90%, and there was no difference between treatments (Qvar 50 μg: 91.6±26.9%; Qvar 100 μg: 91.3±38.5%; placebo: 92.6±39.0%)

Exercise

The primary efficacy variable was the maximum percentage fall in FEV1 following exercise. A statistically significant treatment effect was seen (p=0.038), with no significant period or carry-over effect or difference between the two BDP doses (table 1). AUC for the percentage fall was also greater for placebo compared with HFA-BDP, and a significant treatment effect was found (p=0.003). The AUCs (95% CI) for the three periods were: 351% minimum (237–465) after placebo; 228% minimum (153–303) after BDP 50 μg, and 196% minimum (125–267) after BDP 100 μg. In the pairwise comparisons, both BDP doses were better than placebo (p<0.05). No statistically significant differences were seen between the two BDP doses. The conclusions for maximum percentage fall in forced mid-expiratory flow ($FEF_{25–75\%}$) and AUC for the percentage fall in $FEF_{25–75\%}$ after exercise were very similar to the conclusions for FEV1.

Both BDP doses improved pre-exercise FEV1 significantly (p<0.05) by ~6% pred. Pre-exercise FEV1 (95% CI) during the three periods were 86.8% (82.7–90.9) after placebo, 90.2% (86.1–94.3) after 50 μg BDP, and 90.5% (86.7–94.3) after 100 μg BDP. Similar conclusions were found for pre-exercise $FEF_{25–75\%}$, which was improved by ~20% with both HFA-BDP doses. There was no correlation between increases in FEV1 and reductions in post-exercise fall in FEV1. FEV1 decreased >15% after exercise in 16 out of 25 patients in the placebo group, and 14 out of 25 in both treatment groups.

FEV1 % pred (95% CI) after exercise was 62.4% (58.7–66.1) after placebo, 71.4% (68.0–74.8) after BDP 50 μg, and 71.6% (68.0–75.2) after BDP 100 μg. Calculated in this way, the treatment effect was smaller, but still statistically significant (p=0.049) with no significant period or carry-over effect or difference between the two BDP doses.

Exhaled nitric oxide

Mean eNO levels after HFA-BDP treatment were approximately half the levels seen after placebo (p<0.0001; table 1).

In the pairwise comparisons, significant differences were seen between the two BDP doses and placebo (p<0.05), but no differences between the two BDP doses.

A statistically significant correlation was seen between eNO and the maximum percentage fall in FEV1 (p=0.012) and maximum percentage fall in $FEF_{25–75\%}$ (p=0.010) after placebo treatment (fig. 1). These correlations were no longer statistically significant after HFA-BDP treatments. The results were exactly similar for the correlations between placebo eNO and the AUC fall in FEV1 (p=0.024) and $FEF_{25–75\%}$ (p=0.017).

In total, 17 patients had allergic asthma and eight had nonallergic asthma. As a result of the low numbers, no statistical comparison was made between the two groups. The changes in FEV1 % pred post-exercise in the allergic group were 27.6%, 18.8% and 19.8% after placebo, 50 and 100 μg BDP; the corresponding values for the nonallergic group were 20.6%, 17.1% and 14.9%, respectively. The eNO values in the allergic group were 16.6, 10.7 and 9.8 ppb; the corresponding values for the nonallergic group were 10.2, 6.5 and 7.2 ppb, respectively.

The asthma was mild and the patients reported few asthma problems during placebo treatment. Neither dose of HFA-BDP had any statistically significant effects on PEF, asthma symptom and sleep disturbance scores, or the use of inhaled short-acting β-agonist.

Few patients reported adverse events during treatment: HFA-BDP 50 μg (n=1), HFA-BDP 100 μg (n=4), or placebo (n=3). Adverse events associated with the respiratory system were the most common, and they occurred most frequently with placebo (n=3) compared with HFA-BDP 50 μg (n=1) and HFA-BDP 100 μg (n=1). No adverse events were considered to be associated with the study medication.

Discussion

The present findings showed that a short course of low-dose HFA-BDP exerted a significant reduction in airway hyperreactivity to exercise in children with mild intermittent or mild persistent asthma. This corroborates the findings of other studies with low doses of budesonide or fluticasone propionate in children with mild asthma [1–5]. However, the magnitude of the protective effects in these studies seemed greater than the effects achieved in the present study. Thus, budesonide 100 or 200 $\mu g \cdot day^{-1}$ given either *q.d.* or *b.i.d.* reduced the post-exercise fall in lung function from ~25% to 5–7% [3], and fluticasone propionate 100 μg *b.i.d.* from 33%

Table 1. – Exercise challenge: forced expiratory volume in one second (FEV1) parameters and pre-exercise exhaled nitric oxide (eNO) during the various study periods

	Maximum % fall in FEV1	eNO ppb
Subjects n	25	25
Run-in	31.0±15.3 (24.7–37.3)	16.0±10.1 (11.8–20.2)
Placebo	27.9±15.6 (21.4–34.3)	14.4±9.3 (10.5–18.4)
HFA-BDP 50 μg	20.8±11.2 (16.2–25.4)	9.3±6.8 (6.5–12.1)
HFA-BDP 100 μg	20.9±13.1 (15.5–26.4)	8.9±6.6 (6.2–11.6)
Pairwise differences		
50 μg and placebo	-7.0±16.6 (-13.9–-0.2)	-5.0±6.8 (-7.9–-2.1)
100 μg and placebo	-6.9±13.4 (-12.4–-1.4)	-5.4±7.2 (-8.5–-2.4)
100 μg and 50 μg	0.1±15.5 (-6.2–6.5)	-0.4±3.5 (-1.8–1.0)
p-Values of effects		
Treatment	0.0387	<0.0001
Period	0.2228	0.8349
Carry-over	0.1308	0.2022

Data are presented as n and mean±SD (95% confidence interval). ppb: parts per billion; HFA-BDP: hydrofluoroalkane-beclomethasone dipropionate.

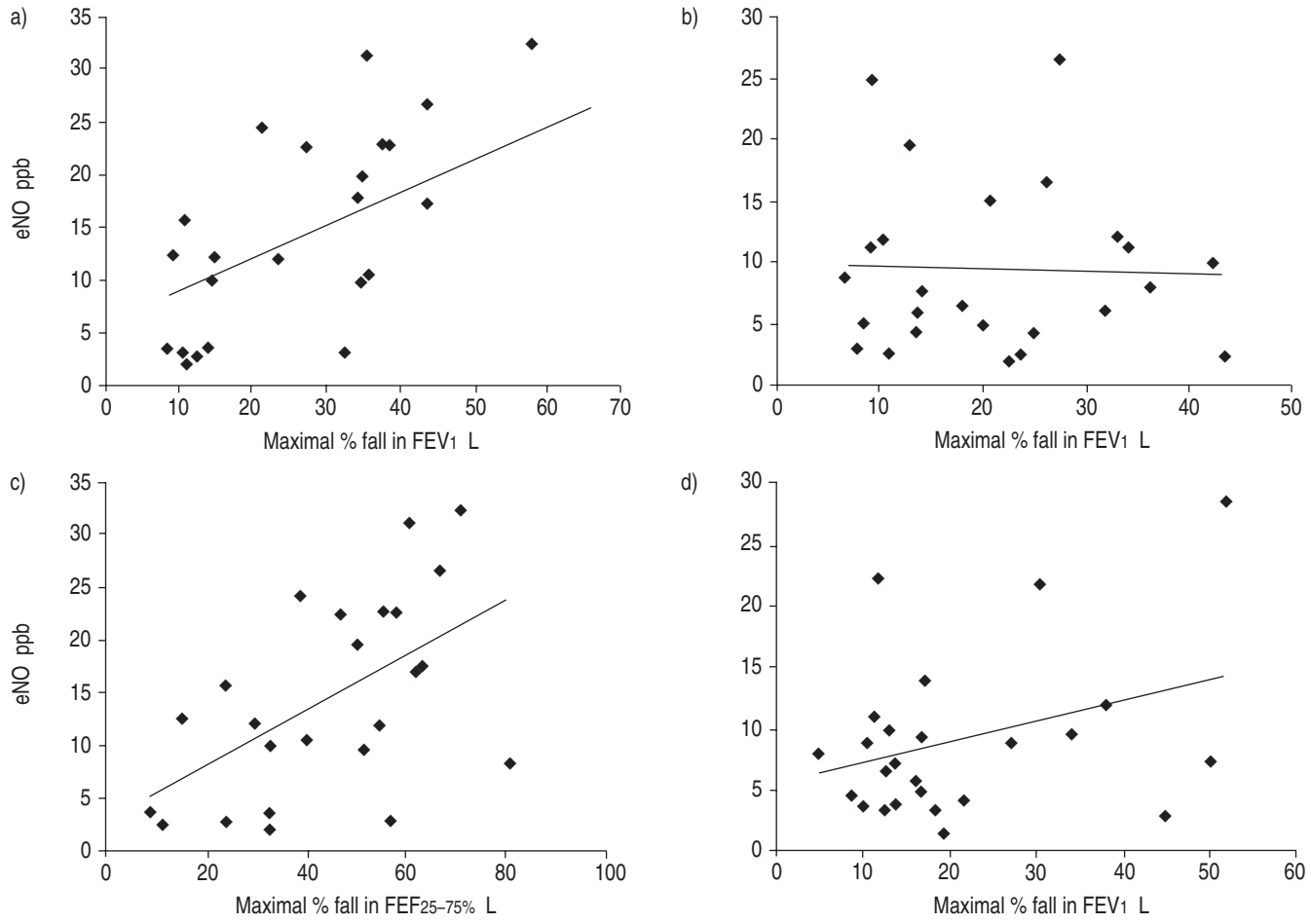

Fig. 1. – Correlation between exhaled nitric oxide (eNO) and maximal % fall in forced expiratory volume in one second (FEV_1) and forced mid-expiratory flow ($FEF_{25–75\%}$) after exercise. Correlation coefficients between eNO and the maximal % fall in FEV_1 for placebo (a; p=0.012) and between eNO and the maximal fall in $FEF_{25–75\%}$ for placebo (c; p=0.010) were calculated. Correlation coefficients for 50 (b) and 100 μg (d) hydrofluoroalkane-beclomethasone dipropionate *q.d.* with FEV_1 were not significant (p>0.05). ppb: parts per billion.

to 9% [5]. In the studies with budesonide, the protective effect of the drug was the same whether it was administered *q.d.* or *b.i.d.* In light of these findings, it was surprising that the fall in FEV1 after exercise was only reduced from 28% to 21% in the present study, considering that the Autohaler used delivers twice as much drug to the intrapulmonary airways as budesonide Turbuhaler [13–18, 20, 24], and at least three times as much as the fluticasone propionate pressurised metered-dose inhaler [15, 17–20, 24] in both children and adults. The reason for this is not clear. One possibility could be that the increased and more peripheral lung deposition from Autohaler was not associated with a similar increase in clinical effect. This seems unlikely, since several studies in children and adults using other outcomes have found increased clinical effects from Autohaler, as compared with less effective delivery devices [25–29]. Another reason could be that BDP is not suitable for *q.d.* administration. No other studies have dosed BDP *q.d.* In the current study, it was always administered in the evening and the exercise challenge was performed in the afternoon on the following day. This may have been too long an interval for a good protection; further studies are needed to assess this. Poor compliance could not explain the rather small effect. It is also unlikely that the treatment duration was too short, since the maximum protective effect is already achieved after 1–2 weeks treatment [30].

Normally, a marked clinical effect is seen at low doses of an ICS, and, often, a four-fold increase in dose is required to produce an additional statistical improvement in an asthma outcome [1], so it might not be surprising that no differences were found between the two BDP doses used in the present study. However, the ICS dose-response curve for protection against exercise-induced bronchoconstriction may be different from the dose-response curves for other outcomes [1, 5, 9–12], and statistically significant differences in protective effects between doubling doses of ICS have been reported earlier in children with moderate and severe exercise-induced asthma [1], even if the lowest dose produced a 50% reduction in the post-exercise fall in FEV1. Therefore, the current authors would have expected to find a dose-response relationship in protective effects against exercise-induced bronchoconstriction, particularly because there was still room for improvement after the low dose: perhaps this was also due to the *q.d.* dosing? An additional dose of HFA-BDP of 200 μg *q.d.* might have elucidated this, but an extra treatment period would have been elusive.

The children selected for this study had mild, intermittent or persistent asthma, and a history of clinically important exercise-induced bronchoconstriction. The diary card data confirmed the mildness of the disease. Almost no symptoms and β-agonist rescue therapy were reported and peak flows were normal. There was virtually no room for improvement in

these parameters. Therefore, it was not surprising that the active treatments were not associated with any statistically significant effects on these outcomes. In contrast, pre-exercise values of FEV1 and FEF25–75% were somewhat reduced, and both doses of BDP caused significant improvements in these outcomes by ~5 and 20% pred, respectively. For these outcomes, it was not surprising that dose-response effects could not be demonstrated: there was little room for improvement after the lowest dose. Lung function was close to normal after that dose.

To evaluate a possible link between the therapeutic effect on airway hyperreactivity and on airway inflammation, levels of eNO were measured pre-challenge. The effects of HFA-BDP on eNO were very similar to the protective effects on exercise-induced bronchoconstriction, except that the lowest dose seemed to have a somewhat greater effect on eNO. Levels of eNO were not normalised (in the current authors' laboratory, normal values are $\leqslant 5$ ppb) and no dose response was seen. Interestingly, significant correlations between eNO and fall in FEV1 or FEF25–75% after exercise were only seen during run-in and after placebo treatment, but not during treatment with BDP. This suggests that the BDP dose-response curves for these two outcomes may be different. Further studies are needed to assess that, but perhaps a more peripheral deposition of drug in the airways is more important for eNO than for protection against exercise-induced bronchoconstriction. The fall in lung function after exercise and the eNO levels were numerically greater in patients with allergic asthma than in children with nonallergic asthma. However, the low number of nonallergic patients precluded any firm conclusions about these differences or potential differences in treatment effects. Further studies are required to assess this.

Conclusion

Low *q.d.* doses of hydrofluoroalkane-beclomethasone dipropionate extra-fine aerosol (50 or 100 μg) reduced exhaled nitric oxide and improved lung function and exercise tolerance in children with exercise-induced asthma. No dose-response effects were seen. Further studies are needed to assess whether *q.d.* administration of beclomethasone dipropionate is as effective as *b.i.d.* administration.

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