

Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma

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Background: Inhaled corticosteroid therapy improves exercise symptoms in asthmatic subjects.

Objective: We sought to evaluate exercise-induced bronchoconstriction (EIB) as a method of determining the dose and time responses of inhaled corticosteroid therapy.

Methods: In this double-blind, randomized, cross-over study with 2 parallel arms, 4 doses of inhaled ciclesonide (40 µg and 160 µg or 80 µg and 320 µg) were compared over 3 weeks of treatment. Twenty-six asthmatic subjects (age range, 14-27 years) with baseline FEV₁ values of greater than 70% of predicted value were enrolled. The primary outcome was the maximum percentage decrease in FEV₁ after standardized exercise challenge.

Results: After 1 week of therapy, the mean ± SEM reduction in maximum decrease in FEV₁ in the ciclesonide 40-µg/80-µg dose group was 9% ± 2.6% (95% CI, 3.9% to 14%), with no additional reduction thereafter. In the ciclesonide 160-µg/320-µg dose group, there was an 8.7% ± 2.5% (95% CI, 3.7% to 13.7%) reduction in maximum decrease in FEV₁ after week 1, which continued in a linear fashion during subsequent weeks of treatment. No difference was found between the 2 treatment arms in the temporal response of EIB to ciclesonide treatment. The maximum percentage attenuation in EIB achieved was 51.1% ± 7.9%, which was achieved by using the 320-µg dose after 3 weeks of treatment.

Conclusions: A significant improvement in EIB was demonstrated for all doses of ciclesonide. Use of 160 µg/320 µg of ciclesonide resulted in a continuing improvement in FEV₁

with time, and no plateau was seen in protective effect during 3 weeks of treatment.

Clinical implications: Attenuation in exercise-induced decrease can be seen as early as after 1 week of therapy with inhaled ciclesonide at doses greater than 40 µg. However, maximal attenuation in exercise response continues to increase at doses greater than or equal to 200 µg, even after 3 weeks of therapy. (J Allergy Clin Immunol 2006;117:1008-13.)

Key words: Asthma, exercise induced, inhaled corticosteroids, randomized controlled trial, dose response

Exercise is a potent cause of acute airway obstruction in asthmatic subjects. Exercise-induced bronchoconstriction (EIB) occurs in 70% to 80% of all asthmatic subjects.¹ Inhaled corticosteroids (ICSs) are the mainstay of therapy for persistent asthma (Global Initiative for Asthma 2004), and although regular therapy with ICSs can decrease the magnitude of EIB, this tends to occur after resolution of daily symptoms and improvement in FEV₁.² The maximum effect of ICSs on exercise response can be reached as quickly as 3 weeks after initiation of therapy.³⁻⁶ However, the exact time at which ICSs exert maximal benefit on the exercise response remains unknown.

Despite ICSs being extensively used as first-line therapy for the treatment of asthma, it has been difficult to demonstrate a dose-response improvement with ICS doses that differ by less than 4-fold.^{2,7-9} Exercise challenge might be one way to demonstrate a dose-response relationship for ICSs because previous studies^{5,6} have suggested incremental but incomplete protection after 3 to 4 weeks of therapy. Thus we hypothesized that if the protection afforded by ICSs was studied at earlier time points, when there is incomplete protection, we might be able to demonstrate a difference between doubling doses of ICSs, which has been difficult to do with other bronchial provocations tests for asthma.

Ciclesonide is a new ICS that is activated by esterases in the airways and achieves high local concentrations in the lungs with very limited systemic exposure.^{10,11} This study evaluated the time course and degree of protection against EIB achieved with 4 doses of inhaled ciclesonide (40 and 160 µg and 80 and 320 µg) treatment administered in a double-blind randomized trial. We chose to quadruple the dose in each group to confirm that the model was

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Some of the data from this article have been presented in abstract form at the American Academy of Allergy, Asthma and Immunology Meeting, San Antonio, Tex, March 2005, and the American Thoracic Society Meeting, San Diego, Calif, May 2005.

Supported in part by Altana Pharma AG, Germany.

Disclosure of potential conflict of interest: S. Pedersen has consultant arrangements with Altana and GlaxoSmithKline and has received grants from AstraZeneca, Altana and GlaxoSmithKline. P. O'Byrne has consultant arrangements with Altana, AstraZeneca, Biolipox, GlaxoSmithKline, Oxygen, Topigen and Roche and has received grants from Altana, AstraZeneca, Biolipox, GlaxoSmithKline, and Pfizer. The rest of the authors have declared that they have no conflict of interest.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2005.11.048

Abbreviations used

AUC: Area under the curve
EIB: Exercise-induced bronchoconstriction
ICS: Inhaled corticosteroid
PEF: Peak expiratory flow

able to detect differences between doses; the group was then divided into parallel arms to examine whether doubling-dose differences between arms (40 and 160 µg and 80 and 320 µg) could be detected.

METHODS

Subjects

Nonsmoking subjects with stable mild asthma (prebronchodilator FEV₁ >70% of predicted value),¹² age 12 to 30 years, and using only short-acting β₂-agonists for rescue therapy were recruited to participate in this study. Exclusion criteria included concomitant history of severe disease precluding the use of ICSs, history of other chronic lung disease, current smokers or exsmokers with more than a 10 pack-year history, recent pulmonary exacerbation or respiratory tract infection (within 6 weeks), or recent initiation of immunotherapy (within 3 months). Eligible patients with a greater than 15% decrease in FEV₁ after a standardized dry-air exercise challenge at a screening visit were invited to participate in the study.

Study design

This trial consisted of 2 parallel, double-blind, double-dummy, randomized controlled crossover study arms; each arm compared 2 doses of ciclesonide (40 and 160 µg and 80 and 320 µg, Fig 1). After a standardized exercise challenge, subjects experiencing a greater than 15% decrease in FEV₁ returned after a 7-day run-in period for a repeat baseline exercise challenge. Only subjects with a maximum decrease in FEV₁ of greater than 15% on their second exercise challenge were enrolled in the study.

After randomization, the subjects received 3 weeks of therapy with inhaled ciclesonide of either 40 and 160 µg or 80 and 320 µg. A standardized dry-air exercise challenge was performed weekly for 3 weeks. The subjects received 2 metered-dose inhaler devices containing either placebo or ciclesonide and were instructed to take 1 puff from each inhaler (patients were instructed on metered-dose inhaler use) administered in the evening. No inhalers were used for 12 hours before exercise testing. Subjects also recorded peak expiratory flow (PEF), daily and rescue medication use, and symptoms in a diary card.

The first study period was followed by a 3-week washout period during which subjects refrained from using any ICS medications. At the end of this period, they returned to the laboratory to perform a standardized dry-air exercise challenge. For entry into the second study period, each subject's maximum decrease in FEV₁ had to be greater than 12%; if their maximum decrease in FEV₁ did not reach 12%, they were asked to return within 2 weeks for a repeat challenge. This was repeated either until their maximum decrease in FEV₁ reached 12% or a total of 8 weeks had elapsed since the last visit of the first study period, at which point they were discharged from the study.

This study was approved by the Research Ethics Board of the Hamilton Health Sciences Corporation and McMaster University under the ICH Good Clinical Practice (GCP) guidelines, and all patients provided written informed consent before starting the study.

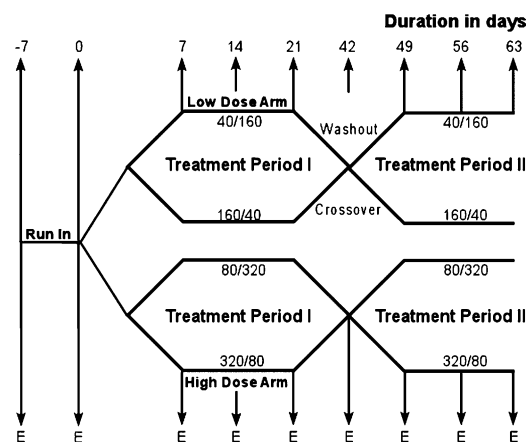


FIG 1. Study design. Outline of study design. E, Exercise protocol performed to measure severity of EIB.

Dry-air exercise challenge

Subjects were asked to refrain from using antileukotrienes for 4 weeks, long-acting β₂-agonists and antihistamines for 3 days, chromones and inhaled anticholinergics for 24 hours, and short-acting β-agonists for 8 hours before the challenge at study entry. Only short-acting inhaled β₂-agonists were allowed as rescue medication during the study period. Only subjects with reproducible spirometric (America Thoracic Society criteria reference) measurements and a baseline FEV₁ of greater than 70% of predicted value¹² were challenged.

The exercise challenge was an 8-minute treadmill (Pacemaster Proplus II; Aerobics Inc, West Caldwell, NJ) test, with continuous heart rate monitoring (Polar Electro Chestband OY, Kempele, Finland). Dry air (temperature 21%, relative humidity <10%, obtained from a compressed air supply and stored in two 100-L Douglas bags) was inhaled by using a face mask (Hans-Rudolph, Kansas City, Mo) with an inspiratory and expiratory valve. The treadmill incline was set at 10%, and the speed was adjusted to achieve a maximum heart rate (210 minus age) of more than 90% of predicted value for the last 4 minutes of the test. After this, the speed was reduced to a comfortable pace while the subject continued to breathe dry air for a further 2 minutes. Lung function was measured at 2, 4, 6, 8, 10, 15, 20, and 30 minutes after exercise. The severity of EIB was expressed as the maximum decrease in FEV₁ after the challenge, which was calculated as follows:

$$\frac{([\text{Pre-exercise FEV}_1 - \text{Lowest FEV}_1 \text{ after exercise}] / \text{Pre-exercise FEV}_1) \times 100.}$$

Statistical analysis

The statistical package SPSS version 12.0 (SPSS, Inc, Chicago, Ill) was used to perform all of the analyses. This study was designed as a pilot study of 24 subjects because inadequate data were available on the variation of the difference in attenuation in maximal exercise response caused by inhaled steroid therapy. Summary statistics were expressed as means and SEMs. FEV₁ and PEF values were expressed as a percentage of predicted values.¹² Attenuation in maximum decrease in FEV₁ or degree of protection in EIB response was expressed as follows:

$$\frac{([\text{Maximum decrease in FEV}_1 \text{ week 1, 2, or 3} - \text{Maximum decrease in FEV}_1 \text{ baseline}] / \text{Maximum decrease in FEV}_1 \text{ baseline}) \times 100.}$$

TABLE I. Baseline demographics

	Overall group, n = 26	Lower-dose arm (40 µg/160 µg), n = 14	Higher-dose arm (80 µg/320 µg), n = 12
Baseline characteristics, mean ± SD (minimum-maximum)			
Sex, M/F	14/12	9/5	7/5
Age, y	19.7 ± 3.4 (14-27)	20.2 ± 3.7 (14-27)	19.1 ± 3.2 (15-27)
FEV ₁ , L	3.7 ± 0.8 (2.5-6.1)	3.7 ± 0.7 (2.8-4.9)	3.7 ± 1 (2.5-6.1)
FEV ₁ , % predicted	92.3 ± 14 (70-122)	93.7 ± 13 (70-114)	90.7 ± 16 (74-122)
FVC, L	4.6 ± 1.0 (3.1-7)	4.5 ± 0.8 (3.1-5.9)	4.7 ± 1.3 (3.2-7)
FVC, % predicted	96.2 ± 10.8 (74-117)	95.1 ± 11.6 (74-115)	97.5 ± 10 (84-117)
FEV ₁ /FVC ratio, %	81.3 ± 8.5 (61-99)	84 ± 8 (69-97)	79 ± 8.9 (61-91)
Maximum decrease in FEV ₁ , %	-31.0 ± 13 (-15 to -63)	-30.6 ± 14 (-16 to -63)	-31.4 ± 12 (-15 to -48)

FVC, Forced vital capacity.

An intention-to-treat model (all subjects randomized to therapy) was used in all analyses. To compare the dose-time response of the maximum decrease in FEV₁, area under the curve (AUC), and attenuation in FEV₁ to therapy, a multiplicative ANOVA model was used with the following factors: dose, arm (40/160 µg of ciclesonide vs 80/320 µg of ciclesonide), visit, and order of therapy. In this analysis the dependent factor (maximum decrease in FEV₁, AUC, or attenuation in FEV₁) at each dose and time point was compared. When the overall ANOVA showed a significant difference, further exploratory analyses with contrasts were performed to explore the specific doses and visits. A mixed-effect regression model was used to examine the rate of improvement in the exercise response over time and by dose by using the arm and order. For all analyses, a *P* value of less than .05 was considered statistically significant.

RESULTS

Twenty-seven mildly symptomatic asthmatic subjects (16 male; mean age, 20 years; age range, 14-27 years), were eligible for enrollment in this study. One female subject experienced an asthma exacerbation caused by a viral illness requiring oral steroid therapy during the run-in period and was excluded from analysis. Fourteen subjects were allocated to the ciclesonide 40/160-µg dose group, and 12 subjects were allocated to the ciclesonide 80/320-µg dose group. In the ciclesonide 40/160-µg dose group, there were 2 dropouts: one male subject did not experience EIB after the first treatment period and thus did not meet the criteria to enter the second period, and a female subject was unable to perform the final exercise challenge because of a musculoskeletal injury. Baseline characteristics were similar between the high- and low-dose arms (Table I).

Overall, there was a statistically significant reduction in the severity of EIB over time with ICS therapy. A significant reduction in maximum decrease in FEV₁ was apparent even after just 1 week of inhaled ciclesonide (*P* < .05) for all except the lowest dose (40 µg, *P* = .09; Table II and Fig 2). By the second week of therapy, there was a significant reduction in EIB severity at all doses of ciclesonide (*P* < .05). The mean percentage ± SEM maximal decreases in FEV₁ after exercise at baseline and weeks 1, 2, and 3 are presented in Table II. After the first

week of therapy, there was no further statistically significant attenuation in maximum decrease in FEV₁ when compared week by week, except for 320 µg of ciclesonide. Similar results were seen when the AUC was examined (Table II).

The mean ± SEM reduction in the maximum decrease in FEV₁ at daily doses of ciclesonide of 40 µg or 80 µg was 9% ± 2.6% (95% CI, 3.9% to 14%) at week 1, with no additional improvement during the subsequent weeks. At daily doses of 160 µg or 320 µg, there was an 8.7% ± 2.5% (95% CI, 3.7% to 13.7%) reduction in the maximum decrease in FEV₁, which continued in a linear fashion during subsequent weeks of treatment. No difference was found in the temporal responses between the 2 arms.

The results were similar for the degree of protection of ciclesonide against EIB. The least attenuation in maximum decrease in FEV₁ (mean ± SEM) achieved was 13.4% ± 15% after 1 week of treatment with the 160-µg dose. By contrast, the greatest attenuation achieved was 51.1% ± 7.9% after 3 weeks of treatment with the 320-µg dose (Table II and Fig 3).

Doubling the dose of ciclesonide did not result in significant differences in EIB. However, after 3 weeks of therapy, there was a significant difference between the protection in decrease in FEV₁ after exercise afforded by quadrupling doses of ciclesonide, being 21.8% ± 4.3% for the 40-µg dose compared with 18.2% ± 3.8% for the 160-µg dose and 19% ± 3.1% for the 80-µg dose compared with 13.4% ± 2.7% for the 320-µg dose (*P* = .04). There were no significant differences between doses in symptom-free days, use of rescue medication, or baseline lung function (FEV₁, FEV₁ percent predicted, or FEV₁/forced vital capacity ratio).

DISCUSSION

To our knowledge, this is the first study examining dose and time responses of low-dose ICSs in patients with EIB during the first 3 weeks of therapy. EIB was attenuated as early as 1 week after initiation of inhaled ciclesonide at doses greater than 40 µg/d. Moreover, the improvement continued to increase in a linear fashion throughout the

TABLE II. Ciclesonide dose-response changes in EIB parameters over time

Arm	Dose		% Maximum decrease in FEV ₁ (mean ± SE)	AUC (mean ± SE)	% Attenuation in maximum decrease in FEV ₁ (mean ± SE)	FEV ₁ , % predicted (mean ± SE)	FEV ₁ /FVC ratio (mean ± SE)
Low	40 µg	Baseline	28.4 ± 3.7	602.4 ± 114		91 ± 3.5	83.2 ± 2.3
		Week 1	23.5 ± 4	363.6 ± 79.9*	22.1 ± 7.8	92.7 ± 3.3	84.3 ± 2.2
		Week 2	20.1 ± 4.2*	338.6 ± 99.3*	33.4 ± 8.5	93 ± 3.4	84.8 ± 2.4
		Week 3	21.8 ± 4.3*	468.2 ± 118*	24.1 ± 9.9	92 ± 3	84.1 ± 2.3
High	80 µg	Baseline	27 ± 3.6	533.5 ± 90.4		87.6 ± 4.1	76.4 ± 2.5
		Week 1	17.7 ± 3.3*	296.1 ± 67.1†	33.1 ± 9.8	89.4 ± 4.2	77.8 ± 2.3
		Week 2	18.2 ± 3*	319.9 ± 65.1*	28.6 ± 9	90 ± 4.6	77.9 ± 2.6
		Week 3	19.1 ± 3.2*	340.6 ± 61.6*	21.5 ± 12.5	89.6 ± 4.6	78.3 ± 2.8
Low	160 µg	Baseline	30.1 ± 4.6	653.3 ± 127		93 ± 2.8	85.1 ± 2.1
		Week 1	25.6 ± 5*	506 ± 136†	13.4 ± 15	92.7 ± 2.7	83.4 ± 2.2
		Week 2	18 ± 4.8*	359.4 ± 127*	40.7 ± 13.3	91.7 ± 2.6	85 ± 2.2
		Week 3	18.2 ± 3.8*	345.9 ± 87*	39.3 ± 9.2	91.6 ± 2.8	84.3 ± 1.8
High	320 µg	Baseline	29.9 ± 4.0	624.2 ± 107		88.4 ± 4	77.7 ± 2.6
		Week 1	21.2 ± 5.1*	404.4 ± 126*	36.1 ± 8.8	89.7 ± 4.5	78.7 ± 2.5
		Week 2	16.2 ± 3.7*	282.3 ± 84.2*	47.9 ± 6.8	89.8 ± 4.2	82 ± 2.5
		Week 3	13.4 ± 2.7*	222 ± 50.9*	51.1 ± 7.9	90.5 ± 4.2	79 ± 2.5

**P* < .05 compared with baseline value.

†*P* < .1 compared with baseline value.

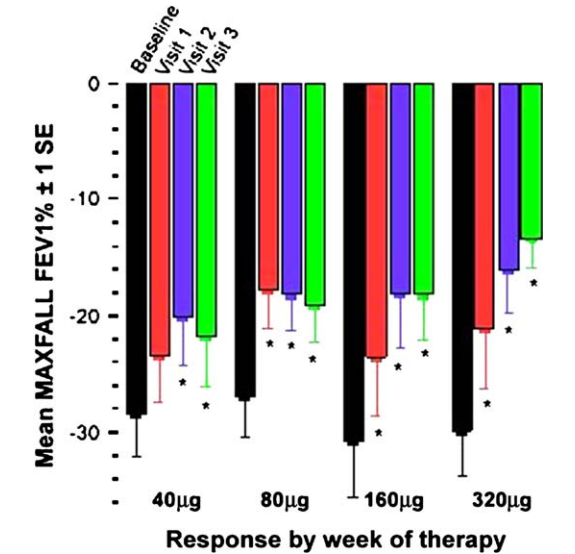


FIG 2. Maximum decrease in FEV₁ (MAXFALL) after exercise by dose. The maximum decrease in FEV₁ decreased after 1 week of therapy in all but the 40-µg dose group and in all groups at subsequent weeks. There was no difference between doubling doses. Rate of improvement in the low-dose groups (40/80 µg) plateaued after 1 week of therapy while continuing to improve weekly in the high-dose groups (160/320 µg). **P* < .05.

3 weeks of treatment with ciclesonide doses of 160 and 320 µg. Although all periods achieved a 30% attenuation in EIB by week 2, only the ciclesonide 320-µg period reached a clinically important degree of protection ($\geq 50\%$) by the third week of therapy. However, the time-response curve in the ciclesonide 160-µg group suggested that if treatment had been continued, a clinically

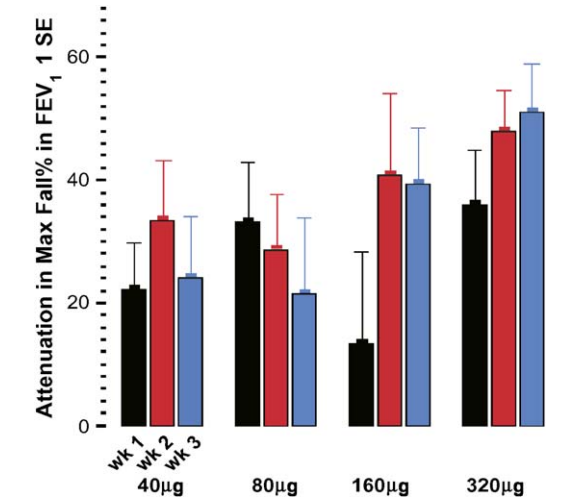


FIG 3. Attenuation in maximum exercise-induced decrease in FEV₁ by dose and week of therapy. There was a trend toward greater improvement in the 160-µg and 320-µg doses by weeks 2 and 3 compared with the lower-dose groups (40 and 80 µg). Clinically significant protection against EIB was achieved at the 320-µg dose by 3 weeks (51%).

important degree of protection might also have been achieved in this group.

In contrast to previous ICS studies,^{5,6} we found that the time-response curve of the EIB protective effect seemed to differ between the various ciclesonide doses. However, these earlier studies did not examine once-daily dosing or doses of less than 100 µg/d. During the ciclesonide 40/80-µg treatment periods, response to therapy seemed to plateau after the first week and stabilize for subsequent

weeks; conversely, in the ciclesonide 160/320- μ g treatment periods, there seemed to be a linear increase in the rate of improvement per week, which continued over the 3 weeks. Particularly in the group treated with 320 μ g of ciclesonide, ciclesonide treatment continued to progressively attenuate EIB throughout the 3-week treatment period. This suggests a threshold effect in attenuation of EIB with ciclesonide therapy, and thus comparison of doubling doses at low-dose levels, which follow a different dose-response curve than higher doses, might not be possible in studies of short duration (<1 month).

Although we demonstrated, as expected, that lower doses of inhaled ciclesonide provided suboptimal protection against EIB, this clinical model was unable to demonstrate significant differences between doubling doses of ciclesonide. Only one study has been able to show differences between doubling doses of inhaled budesonide (100, 200, and 400 μ g).⁶ In that study the magnitude of the EIB was much greater (approximately 60%) compared with that seen in the present study, and the magnitude of the baseline exercise response might be a significant factor in the sensitivity of the exercise challenge as a model. Although we were able to demonstrate only partial attenuation in the exercise response at the lowest dose and thus are confident that these doses were not on the flat part of the dose-response curve for inhaled ciclesonide, there was a difference in the time response between doses lower than and doses greater than 100 μ g. These differences in the time-response curves between the low-dose and high-dose arms might be one possible explanation for the failure of the model to detect doubling-dose differences. An additional explanation might be inadequate sample size leading to lack of power to detect differences.

In this study we found that the coefficient of variability of the decrease in FEV₁ varied between 15% and 20% during screening, which is similar to that seen in previous studies,¹³ but increased to 30% to 35% with treatment. This increase in variability of the exercise response during treatment suggests that some subgroups of patients might respond better to therapy than others. A retrospective power analysis shows us that the expected difference of 50% was only attained at the 1-week time point in the 200- μ g versus 400- μ g group, but because of the excessive variability of the attenuation in exercise decrease with treatment (SEM, 18%), the power was only 50%. Thus to detect a 50% reduction in attenuation in maximum decrease caused by a doubling-dose difference in ICSs, we would need to recruit at least 60 subjects. The need for such a relatively large numbers of subjects with exercise-induced asthma makes the use of exercise methodology impractical for studies of relative potency unless factors identifying the reasons for increased variability in treatment response can be identified and more uniform groups of patients can be recruited for these types of studies.

We demonstrated that despite 3 weeks of therapy, the magnitude of protection was only 25% in the lower-dose groups and 40% to 50% in the higher-dose groups. These findings are in contrast to other studies suggesting a 60%

to 80% protection in EIB after 3 weeks of therapy.^{5,6,14,15}

One possible reason for this attenuation in protection might be the once-daily dosing strategy. A previous study of 50 μ g and 100 μ g of hydrofluoroalkane-delivered beclomethasone dipropionate administered once daily showed similar levels of protection (approximately 30%) after 4 weeks of treatment.¹⁶ However, in a study with budesonide at 100 μ g/d, the degree of protection was similar whether budesonide was administered once or twice daily.¹⁴ It is unlikely that the mode of delivery accounts for this discrepancy because both this study and the report of Petersen et al¹⁶ used hydrofluoroalkane formulations, which have higher pulmonary drug deposition than the Turbuhaler.^{17,18} Furthermore, previous studies comparing ciclesonide and budesonide have suggested similar efficacy in reducing airway inflammation and airway hyperresponsiveness to adenosine monophosphate challenge,¹⁹ suggesting that it is unlikely that differences in potency would explain these findings. In both the current study and that of Petersen et al,¹⁶ medication was administered in the evening at least 12 hours before the challenge. One study has suggested that there is an acute effect of high doses of ICSs on EIB when administered 4 hours before the challenge,²⁰ suggesting a possible mechanism for the discrepancy in the once-daily and twice-daily dosing regimen. Further studies examining the acute effects of inhaled steroids on the exercise response are needed to clarify this issue.

Finally, despite demonstrating attenuation in the exercise response to a clinically noticeable degree, we were unable to show any changes in PEF, FEV₁, or FEV₁/forced vital capacity ratio after 3 weeks of therapy. This is likely due to the fact that our subjects had only mild lung function impairment at baseline and thus might have been unable to show a marked improvement with therapy. Previous studies have suggested that the dose-response curve for lung function is steeper than exercise response in children, and thus improvement in lung function might be seen before the protection against EIB.^{6,21} However, most of these studies used higher doses (>400 μ g)^{5,21} or longer treatment periods (>3 weeks).⁶

In conclusion, this is the first study to demonstrate attenuation in exercise response as early as 1 week in doses of less than 400 μ g/d ciclesonide. We also demonstrated that the dose-response characteristics over time differed between lower ($\leq$ 80 μ g) and higher ($\geq$ 160 μ g) doses of ciclesonide. We achieved a clinically important degree of protection of between 47% and 51% with 320 μ g/d ciclesonide after 2 to 3 weeks of treatment. Despite demonstrating less than complete protection with all doses of inhaled ciclesonide used in the study, we were unable to show differences in doubling doses of ciclesonide using this exercise challenge model.

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