

Effect of low-dose ciclesonide on allergen-induced responses in subjects with mild allergic asthma

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Background: Inhalation of allergens by sensitized patients with asthma induces reversible airway obstruction, airway hyperresponsiveness, and eosinophilic airway inflammation. Attenuation of allergen-induced bronchoconstriction and inflammation has been used to examine the efficacy of therapeutic agents such as inhaled corticosteroids in asthma. Ciclesonide, a nonhalogenated inhaled corticosteroid being developed for the treatment of persistent asthma, remains inactive until cleaved by esterases in the lung.

Objective: This study examined the effect of low doses of inhaled ciclesonide, 40 µg and 80 µg, on allergen-induced bronchoconstriction, serum eosinophil cationic protein, and eosinophilic airway inflammation.

Methods: Twenty-one nonsmokers with mild atopic asthma completed a multicenter, randomized, 3-way crossover study comparing the effects of 7-day treatment of ciclesonide or placebo. Allergen-induced responses, including the early and late fall in FEV₁, peripheral blood eosinophils, serum eosinophil cationic protein levels, and eosinophils in induced sputum were measured.

Results: Ciclesonide 80 µg attenuated the early and late asthmatic responses, including the change in FEV₁, serum eosinophil cationic protein, and sputum eosinophils measured at 24 hours postchallenge ($P < .025$). Ciclesonide 40 µg attenuated the late asthmatic responses and sputum eosinophils measured at 24 hours postchallenge ($P < .025$), with no effect

on the early allergen-induced bronchoconstriction, 24-hour FEV₁, or serum eosinophil cationic protein levels ($P < .025$). **Conclusion:** With the exception of 24-hour postchallenge peripheral blood eosinophils, a low dose of ciclesonide, 80 µg, was effective in blocking all allergen-induced responses measured. (J Allergy Clin Immunol 2005;116:285-91.)

Key words: Inhaled corticosteroid, allergen inhalation, airway inflammation

Asthma is characterized by reversible airway obstruction, airway hyperresponsiveness, and eosinophilic bronchial inflammation. Subjects with allergic asthma develop an immediate IgE-mediated early asthmatic response (EAR) after inhalation of an allergen to which they are sensitized. Approximately 50% of these subjects also develop a late asthmatic response (LAR), which begins 3 to 4 hours after allergen inhalation.¹ The LAR is associated with elevated levels of airway inflammatory cells including eosinophils, basophils, and mast cells.^{2,3} This model of allergen-induced bronchoconstriction has been used successfully to assess drug efficacy in subjects with allergic asthma⁴⁻¹³ and is recommended for evaluation of inhaled corticosteroids (ICS).¹⁴

Inhaled corticosteroids, having potent anti-inflammatory properties, are indicated by the Global Initiative for Asthma as a primary controller for treatment of mild-persistent to severe asthma.¹⁵ Studies of ICS have consistently shown a significant attenuation of the allergen-induced LAR,^{5,16-18} with the proposed mechanism attenuation of the allergen-induced airway inflammation. However, undesirable side effects of ICS at higher doses have established a need to evaluate ICS properties at very low doses.¹⁴

Ciclesonide is a nonhalogenated ICS for the treatment of persistent asthma of all severities. This ICS remains inactive until cleaved by esterases present in the airway, where its active metabolite, desisobutryl-ciclesonide, then binds glucocorticoid receptors.

Before developing an optimal solution for metered dose inhaler (MDI) formulation for clinical use, early clinical studies were performed with ciclesonide by using a dry powder inhaler (DPI) device. One week of ciclesonide 800 µg DPI BID (twice daily; using Cyclohaler device [Pharmachemie, Haarlem, The Netherlands]) has been

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Abbreviations used

AE:	Adverse event
AUC _{0-2h} :	Area under the curve of the early response
AUC _{3-8h} :	Area under the curve of the late response
BID:	Twice daily
DPI:	Dry powder inhaler
EAR:	Early asthmatic response; maximum % fall in FEV ₁ from 0 to 2 hours after allergen challenge
ECP:	Eosinophil cationic protein
ICS:	Inhaled corticosteroids
LAR:	Late asthmatic response; maximum % fall in FEV ₁ from 3 to 8 hours after allergen challenge
MDI:	Metered dose inhaler

shown to attenuate significantly the allergen-induced EAR and LAR,¹⁹ confirming that this drug has biological activity in this model of allergic inflammation. The allergen-induced fall in FEV₁ was shown to be a sensitive marker of dose-response effect in an earlier trial of mometasone furoate¹⁶; therefore, the current trial was performed to examine the dose-response of the LAR and to determine the efficacy of low-dose ciclesonide in the reduction of the allergen-induced EAR, LAR, and airway inflammation. In-house testing has led to the development of ciclesonide in MDI formulation with hydrofluoroalkane (HFA) propellant, delivering 40 µg, 80 µg, and 160 µg (ex-actuator) per puff. However, data are limited regarding what the lowest effective dose is with the MDI formulation of ciclesonide. This study, therefore, was designed to identify the lowest effective dose of ciclesonide in MDI formulation in an allergen inhalation model.

METHODS

Subjects

Thirty-five subjects were enrolled in the study. Of these, 13 patients did not meet randomization criteria. Twenty-two subjects (Groningen, n = 5; Laval, n = 7; McMaster, n = 10), 14 men and 8 women, age 19 to 58 years old (Table I), were randomized to one of the 6 treatment sequences. One subject discontinued the study prematurely for nonmedical reasons. Inclusion criteria required subjects to be nonsmokers with mild atopic asthma, free of other lung disease, and without lower respiratory tract infection for 6 weeks before entering the study. For randomization, subjects were required to have stable asthma with FEV₁ > 70% of predicted; have baseline methacholine PC₂₀ < 16 mg/mL; use no regular asthma medication during the study other than infrequent inhaled β₂-agonist, which was withheld for 8 hours before each visit; and have no exposure to sensitizing allergens apart from house dust mite. Before entering the study, subjects could not have used systemic steroids or had an asthma exacerbation for 6 weeks and could not have used inhaled steroids for at least 4 weeks. Before morning visits to the lab, subjects were to refrain from tea or coffee.

Study Design

This trial was a multicenter, double-blind, randomized, placebo-controlled, 3-period crossover study comparing 7 days of treatment with ciclesonide at 50 µg and 100 µg exvalve, corresponding to

40 µg and 80 µg ex-actuator, with placebo. The study was approved by the ethics research board of the respective institutions, and signed informed consent was given to participate. Screening of subjects was performed over a period of 2 consecutive days and included a detailed history, physical examination, allergen skin test, FEV₁, methacholine PC₂₀, blood sampling for serum ECP levels, allergen inhalation challenge, and sputum induction. Subjects who developed an EAR (at least 20% fall in FEV₁ within 2 hours after allergen inhalation) and LAR (at least 15% fall in FEV₁ between 3 and 8 hours after allergen inhalation) during 1 screening allergen inhalation challenge were enrolled in the study. Subjects were screened once only, because we have shown the LAR to be a reproducible measurement.^{20,21} Subjects reported to the laboratory for 3 separate treatment periods separated by a minimum of 3 weeks (Fig 1). This washout time has been shown to be adequate in a previous study of ICS using this model.¹⁶ Each treatment period consisted of 4 morning visits. Day 1 consisted of pretreatment measurements of blood eosinophils, sputum inflammatory cells, and lung function; methacholine PC₂₀ needed to be within 1 doubling dose of that measured during the screening period to continue with the treatment period. If this criterion was met, subjects then inhaled the first dose of study medication during the morning visit to the lab. The subsequent doses of study medication were inhaled for the next 6 consecutive mornings, immediately after waking, because ciclesonide has been shown to improve asthma control irrespective of the time of administration.²² Subjects returned to the laboratory on day 5 for measurement of preallergen challenge sputum inflammatory cells and on day 6 for allergen inhalation challenge. Measurements of FEV₁ were taken at regular intervals until 8 hours after challenge. On day 7, subjects underwent measurements of sputum inflammatory cells, blood eosinophils, and serum ECP. Postallergen methacholine PC₂₀ was not measured, because this study was not powered sufficiently for this comparison. All subjects were considered compliant with study medication according to the diary cards.

Laboratory procedures

Methacholine inhalation test. Methacholine inhalation challenge was performed as described by Cockcroft.²³ Subjects inhaled normal saline during 2 minutes of tidal breathing, nebulized at 0.13 mL/minute from a Wright nebulizer, then doubling concentrations of methacholine chloride. FEV₁ was measured at 30, 90, 180, and 300 seconds after each inhalation. The test was terminated when a fall in FEV₁ of 20% of the baseline value occurred, and the methacholine PC₂₀ was calculated.

Allergen inhalation challenge. Allergen challenge was performed as described by O'Byrne et al.¹ Subjects were skin tested for allergies to common aeroallergens. The allergen producing the largest skin wheal diameter was diluted in 0.9% saline and stored for subsequent allergen inhalation challenges. The concentration of allergen extract for inhalation was determined from a formula described by Cockcroft et al,²⁴ and doubling concentrations of allergen were given until a <20% early fall in FEV₁ at 10 minutes postallergen was reached. The FEV₁ was then measured at regular intervals until 8 hours after allergen inhalation. The early area under the curve (AUC_{0-2h}) and the late area under the curve (AUC_{3-8h}) were calculated by using the trapezoidal rule, were normalized to 1 hour, and were expressed as liters × hour (L×h). Subjects inhaled the same dose of allergen for the 3 treatment periods.

Sputum analysis. Sputum was induced and processed by using the method described by Pizzichini et al.²⁵ Cell plugs were selected and mixed with 0.1% dithiothreitol (Sputolysin; Calbiochem Corp, San Diego, Calif) and Dulbecco PBS (Life Technologies Inc, Grand Island, NY) and filtered through a 48-µm nylon gauze (BNSH Thompson, Scarborough, Ontario, Canada), and cytopins were

TABLE I. Subject characteristics at study screening visit

Subject	Age (y)	Sex	Predicted FEV ₁ (%)	FEV ₁ /VC ratio	Methacholine PC ₂₀ (mg/mL)	Allergen	Final dose, median
50001	25	F	96	0.86	1.12	Ragweed	1:64
50002	21	M	114	0.86	8.94	HDM	1:16
50004	42	M	106	0.69	4.54	HDM	1:32
50005	20	M	73	0.55	0.31	HDM	1:1024
50008	26	F	89	0.92	1.63	Ragweed	1:16
50011	54	M	107	1.18	0.88	Cat	1:32
50012	33	M	88	0.73	15.51	Ragweed	1:64
50013	54	M	73	0.55	3.39	HDM	1:64
50014	19	F	109	0.83	0.54	HDM	1:128
50015	39	M	80	0.67	5.11	HDM	1:128
50025	26	F	83	0.89	1.07	HDM	1:32
50027	28	F	121	0.87	1.11	Cat	1:64
50028	25	F	96	0.86	1.42	Cat	1:16
50029	23	M	99	0.77	1.47	Cat	1:64
50031	30	M	75	0.70	0.86	Cat	1:128
50032	26	M	93	0.73	2.21	HDM	1:64
50033	38	M	112	0.72	1.56	HDM	1:128
50038	19	M	103	0.84	0.70	HDM	1:1024
50039	58	M	107	0.79	8.80	HDM	1:2048
50040	40	M	84	0.80	0.44	HDM	1:2048
50041	49	F	100	0.86	0.21	HDM	1:2048
50045	33	F	85	0.83	0.33	HDM	1:1024
Mean ± SEM	33.1 ± 2.6	14 M 8 F	95.1 ± 3.0	0.80 ± 0.03	1.46 (15.51-0.21)	14 HDM 5 Cat 3 RW	1:64

HDM, House dust mite; VC, vital capacity.

prepared on glass slides. The total cell count was determined by using a Neubauer hemocytometer chamber (Hausser Scientific, Blue Bell, Pa) and expressed as the number of cells per milliliter sputum, and differential cell counts were obtained from slides stained with Diff Quik (American Scientific Products, McGaw Park, Ill). All slides were enumerated at 1 site. Slide preparation and enumeration were performed before unblinding. The study personnel collecting sputum samples and the technician enumerating the slides had no knowledge of the coding of the labels, nor of the airway physiology measured when these sputum samples were collected. All data were collected centrally and entered into a master database before the random code was distributed to participating sites.

Serum eosinophil cationic protein and blood eosinophils. Blood was collected into 4-mL vacutainer hemogard SST tubes (Becton Dickinson, Franklin Lakes, NJ) for serum separation. Eosinophil cationic protein (ECP) was released by allowing blood to clot for 60 to 120 minutes at room temperature, and then samples were centrifuged at 1000g to 1300g for 10 minutes at room temperature. Serum was removed and stored at -20°C until analysis. All serum ECP was analyzed at 1 site by using the UniCAP system (Pharmacia, Uppsala, Sweden). Blood was also collected into 2-mL EDTA vacutainers, and eosinophil counts were performed by Coulter Counter (Beckman Coulter, Fullerton, Calif) at the respective institutions.

Statistical analysis

The target sample size of 18 patients is sufficient to guarantee a power of 90% in correctly concluding superiority at the .0125 level, 1-sided, if the mean difference accounts for 90% of the SD (based on paired *t* test). The 21 subjects who completed the study were included in the statistical analyses. Summary statistics are expressed as mean

and SEM. Between-treatment differences in FEV₁ during the LAR, FEV₁ during the EAR, and sputum eosinophils 24 hours after allergen were analyzed by using ANOVA. The FEV₁ measured 24 hours after allergen was analyzed with analysis of covariance by using the baseline value as a covariate to test both within-treatment and between-treatment differences. Within-treatment differences in sputum variables as well as between-treatment differences in blood eosinophils, ECP, and sputum variables were analyzed by means of the nonparametric test for 3 × 6 crossover design. One-sided *P* values were generated for all variables, and significance is shown at *P* < .025.

RESULTS

All subjects inhaled the same dose of allergen for the 3 treatment periods. There were no serious adverse events (AEs), and 11 treatment-emergent AEs were reported. Of these, 7 AEs were mild and 4 were moderate. All AEs were assessed as unrelated to the study medication, except 1 case of thrombocytopenia, which was assessed unlikely related to the study medication. No adverse event led to premature discontinuation or a change in study medication. Before allergen challenge, the degree of airway hyperresponsiveness was within 1 doubling dose, and there was no significant difference in FEV₁ between the 3 treatment periods. During placebo treatment, all subjects demonstrated early and late airway responses after allergen inhalation challenge; the maximum percent fall in FEV₁ was 30.4% ± 2.2% during the early response

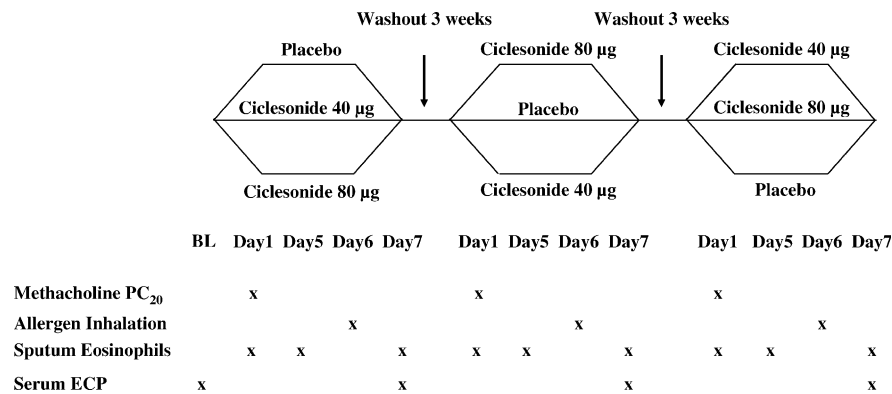


FIG 1. Study schematic. BL, Pretreatment baseline.

 TABLE II. Effect of ciclesonide on the maximum percent fall in FEV₁ and area under the curve of the early and late airway responses

	Placebo	Ciclesonide 40 µg	Ciclesonide 80 µg
EAR (%)	30.4 ± 2.2	28.2 ± 2.2	23.6 ± 2.2*
AUC _{0-2h} (L×h)	-33.3 ± 4.0	-29.2 ± 4.6	-24.9 ± 4.1*
LAR (%)	24.0 ± 2.1	13.3 ± 2.1**	10.7 ± 2.1**
AUC _{3-8h} (L×h)	-27.5 ± 4.3	-11.8 ± 4.0**	-9.4 ± 2.7**

 **P* < .025 compared with placebo.

 ***P* < .013 compared with placebo.

and 24.0% ± 2.1% during the late response, corresponding to AUC_{0-2h} of -33.3 ± 4.0 L×h and AUC_{3-8h} of -27.5 ± 4.3 L×h (Table II).

During treatment with ciclesonide 80 µg, there was a significant reduction in the maximum percent fall in FEV₁ during the EAR to 23.6% ± 2.2% (*P* = .016), the AUC_{0-2h} (*P* = .013), the maximum percent fall in FEV₁ during the LAR to 10.7% ± 2.1% (*P* < .001), and the AUC_{3-8h} (*P* < .001). Treatment with ciclesonide 40 µg significantly reduced the maximum percent fall in FEV₁ during the late response to 13.3% ± 2.1% (*P* = .0003) and AUC_{3-8h} (*P* = .0003), with no significant effect on the early maximum percent fall in FEV₁ or AUC_{0-2h} (*P* > .025). There was no significant difference between ciclesonide 40 µg and 80 µg on the EAR, LAR, AUC_{0-2h}, or AUC_{3-8h} (*P* > .025; Table II).

FEV₁ was measured at pretreatment baseline (day 1), preallergen (day 6), and at 24 hours postallergen inhalation challenge (day 7). With placebo treatment, the FEV₁ of 3.38 L ± 0.17 L at day 7 was significantly lower than the day 1 FEV₁ of 3.60 L ± 0.15 L (*P* < .001) and the day 6 FEV₁ of 3.56 L ± 0.16 L (*P* < .001). During treatment with ciclesonide 40 µg, the FEV₁ of 3.50 L ± 0.16 L at day 7 was significantly lower than that of day 1 or day 6, 3.65 L ± 0.17 L and 3.62 L ± 0.15 L, respectively (*P* < .001). During treatment with ciclesonide 80 µg, the FEV₁

of 3.59 L ± 0.18 L at day 7 was significantly lower than 3.67 L ± 0.18 L at day 1 (*P* = .013), but not significantly different from the FEV₁ of 3.64 L ± 0.16 L at day 6 (*P* = 0.10). Compared with placebo, ciclesonide 80 µg significantly attenuated the day 7 allergen-induced decrease in FEV₁ compared with day 1 (*P* = .002) and day 6 (*P* = .007; Fig 2). Compared with placebo, ciclesonide 40 µg did not attenuate day 7 allergen-induced decrease in FEV₁ compared with day 1 or day 6 (*P* > .025). There was a trend toward a dose-response effect for ciclesonide, with greater attenuation of the 24-hour postallergen fall in FEV₁ by ciclesonide 80 µg compared with ciclesonide 40 µg; however, this did not reach statistical significance (1-sided *P* = .028; Fig 2).

At 24 hours after allergen inhalation challenge, serum ECP increased from a baseline of 20.7 µg/L ± 3.0 µg/L to 31.0 µg/L ± 5.8 µg/L with placebo, 33.0 µg/L ± 5.6 µg/L with ciclesonide 40 µg, and 26.0 µg/L ± 5.3 µg/L with ciclesonide 80 µg. There was significant attenuation of the allergen-induced increase in serum ECP with ciclesonide 80 µg versus placebo treatment (*P* = .024), but no effect of ciclesonide 40 µg. Peripheral blood eosinophils were not significantly reduced with ciclesonide 40 µg or 80 µg (*P* > .025). There was an allergen-induced increase in the number of peripheral blood eosinophils at 24 hours after challenge, increasing from a baseline of 0.294 × 10⁶/mL ± 0.037 × 10⁶/mL to 0.404 × 10⁶/mL ± 0.040 × 10⁶/mL with placebo, 0.385 × 10⁶/mL ± 0.047 × 10⁶/mL with 40 µg ciclesonide, and 0.347 × 10⁶/mL ± 0.052 × 10⁶/mL with 80 µg ciclesonide.

There was an allergen-induced increase in the percent sputum eosinophils (Fig 3, A) and the number of eosinophils per milliliter sputum (Fig 3, B) on day 7 compared with day 5 with placebo, ciclesonide 40 µg, and ciclesonide 80 µg treatment (*P* < .002). However, both ciclesonide 40 µg and 80 µg significantly attenuated the allergen-induced increase in the percentage of sputum eosinophils (*P* < .001 and *P* = .006, respectively). Only ciclesonide 80 µg significantly attenuated the allergen-induced increase in the number of eosinophils per milliliter sputum, but the trend toward a dose-dependent effect

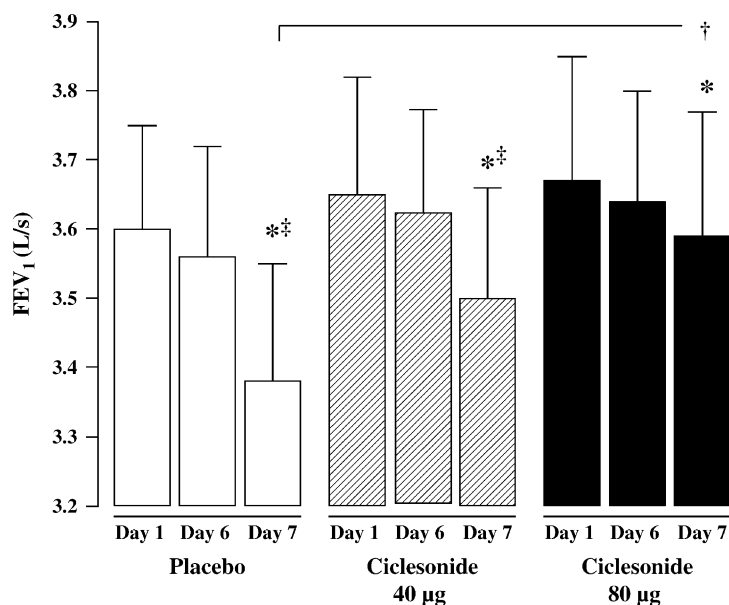


FIG 2. A comparison of FEV₁ measured at day 1 (before treatment), day 6 (after 6 days of treatment), and day 7 (24 hours after allergen inhalation challenge) with placebo (open bars), ciclesonide 40 µg (hatched bars), and ciclesonide 80 µg (solid bars) treatments. * $P < .025$ compared with day 1 pretreatment. ‡ $P < .025$ compared with day 6 preallergen. † $P < .025$ attenuation of allergen-induced increase compared with placebo.

for ciclesonide did not reach statistical significance (1-sided $P = .03$).

DISCUSSION

Ciclesonide is a new generation inhaled glucocorticosteroid that remains inactive until cleaved by esterases present in the lung. Ciclesonide has been shown to be effective to reduce allergen-induced early and late responses when administered at 800 µg twice daily by Cyclohaler (DPI),¹⁹ yet it was unknown whether lower doses of 80 µg or 40 µg administered by MDI would also be effective. In the current study, ciclesonide was administered by MDI once daily for 7 days at considerably lower doses than previously studied.

This study has demonstrated that once-a-day treatment with 40 µg or 80 µg ciclesonide for 7 days is indeed efficacious in this model of allergen-induced bronchoconstriction and airway inflammation. Furthermore, we were able to determine the lowest effective dose of ciclesonide for attenuating all allergen-induced responses investigated in this study. In contrast with the 40 µg dose, ciclesonide at 80 µg per day attenuated the allergen-induced early airway response, the sustained fall in FEV₁ measured 24 hours postchallenge, and the allergen-induced accumulation of eosinophils into the airways. Whether 80 µg represents a plateau beyond which there is no further attenuation of allergen-induced responses is unknown.

Compared with the aforementioned study of 800 µg ciclesonide DPI BID resulting in approximately 51% attenuation in the late fall in FEV₁,¹⁹ 80 µg in the current

study resulted in 58% inhibition and 40 µg resulted in 45% inhibition of the fall in FEV₁ during the late response. The early response was not attenuated as effectively with the lower doses of ciclesonide, with 40 µg and 80 µg providing approximately 8% and 23% inhibition of the early fall in FEV₁, respectively, compared with the 45% inhibition with 800 µg ciclesonide BID previously studied.¹⁹ The deposition pattern of HFA-MDI formulations in the peripheral lung may not inhibit the EAR as effectively compared with the DPI formulation, which gets deposited in the large, central airways where the EAR is likely to be most active. This supports the consistent observation that multiple or single doses of inhaled steroids may significantly attenuate the LAR without significantly attenuating the EAR.^{5,18,26} Moreover, these data suggest that higher levels of HFA-MDI formulation steroids are necessary to inhibit IgE-mediated early responses to inhaled allergen, such as mast cell degranulation, compared with lower levels of steroids that appear to suppress the late response effectively, likely through inhibition of proinflammatory cytokine gene expression.²⁷

Ciclesonide HFA-MDI 200 µg 4 times daily administered in a previous study²⁸ did not affect urine cortisol levels after 4 weeks treatment, which suggests that the 80 µg dose in the current study would have a very low potential for systemic activity. We did not measure systemic safety markers, because no effect would have been expected. It is unknown, however, whether systemic activity in compartments such as the circulation and/or bone marrow is an unidentified yet important site of action of inhaled steroids. There is certainly evidence showing that steroids provide anti-inflammatory effects

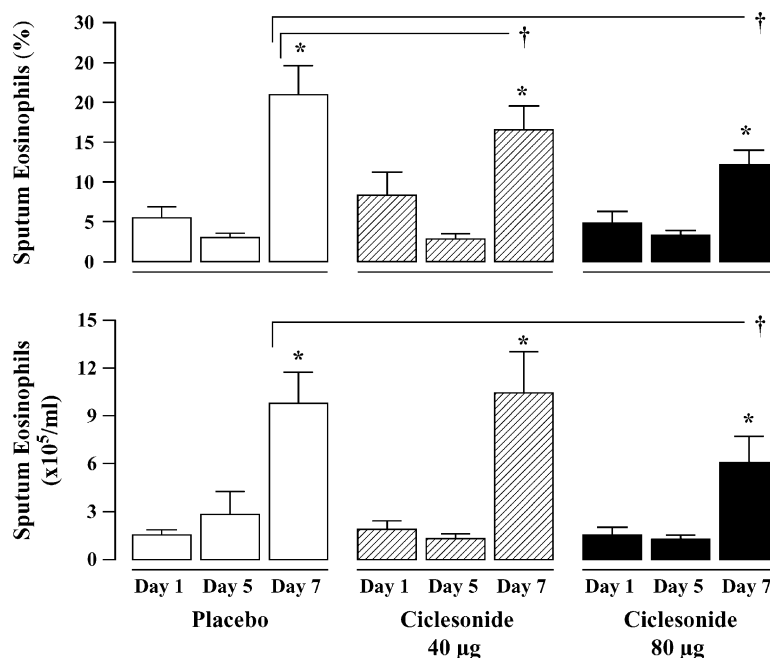


FIG 3. A comparison of percent sputum eosinophils (*top panel*) and number of sputum eosinophils (*bottom panel*) measured on day 1 (before treatment), day 5 (after 5 days treatment), and day 7 (24 hours after allergen challenge) with placebo (*open bars*), ciclesonide 40 µg (*hatched bars*), and ciclesonide 80 µg (*solid bars*) treatments. * $P < .025$ compared with day 5 preallergen. † $P < .025$ attenuation of allergen-induced increase compared to placebo.

in these other compartments.^{17,29} The low potential for systemic activity with low-dose ciclesonide treatment supports the notion that steroid regulation of allergen-induced bone marrow responses is likely through suppression of proinflammatory mediators generated in airways that subsequently control the bone marrow, rather than the belief that steroids have a direct effect on cells in the bone marrow.³⁰ Because new generation steroids are preferred as a result of their low systemic effects, this question of whether some systemic activity is also required will become an important issue that needs to be addressed.

There was a numerical, though insignificant ($P > .025$), dose-response for low doses of ciclesonide during the late response, which is believed to be one of the most sensitive variables used to demonstrate a dose-response.¹⁶ Surprisingly, these data demonstrate dose-responses to measurements of airway obstruction and inflammation at 24 hours postchallenge. This is an unexpected finding, indicating these variables may be worthy of evaluation in subsequent trials evaluating dose-responses.

Although results from this study suggest that 80 µg ciclesonide may be the minimally effective dose for protection against the EAR and serum ECP levels, it is noteworthy that there was a significant effect of both 80 µg and 40 µg ciclesonide on the LAR and percentage of sputum eosinophils. This implies that the minimally effective dose for protection against these parameters is likely to be less than 80 µg. However, during the course of the study, ciclesonide was always administered in the

morning immediately after waking, and approximately 1 hour preallergen challenge. Hence, the drug was present at the highest possible levels during challenges. Whether this degree of efficacy would have been observed had drug administration and allergen challenge been separated by a longer time interval is unknown, but is important to consider, because the protective effects of inhaled steroids against allergen-induced early responses, airway eosinophilia, and allergen-induced airway hyperresponsiveness are partially or completely lost as early as 12 hours after discontinuation of therapy.¹⁸

Direct comparisons between various ICS were not performed in this study, largely because of the difficulties associated with 4-way crossover studies. Although a direct comparison would need to be performed to indicate the relative potency of ciclesonide, the dose of 80 µg appears to be similar to proven effective doses of other inhaled steroids; 50 µg mometasone furoate BID has been shown to attenuate significantly the EAR, LAR, and 24-hour postallergen sputum eosinophils.¹⁶ This study has provided new information regarding the minimally effective doses of inhaled ciclesonide for inhibition of allergen-induced airway responses and the apparent local anti-inflammatory effects on the airways. Further evaluation of ciclesonide will be required to address whether these low doses are clinically effective.

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