Allergy 2003: 58: 207–212
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ALLERGY
ISSN 0105-4538

Original article

Effect of ciclesonide on allergen challenge in subjects with bronchial asthma

Background: The aim of this clinical trial was to investigate whether repeated inhalation of the new inhaled steroid ciclesonide reduces the early-phase (EAR) and late-phase (LAR) reactions after allergen challenge in patients with mild allergic asthma. Also, this study provides further data on safety and tolerance of ciclesonide.
Methods: The study was designed as a double-blind placebo-controlled randomized crossover trial. Following a baseline period, patients were randomized to either of two treatment sequences (ciclesonide/placebo, placebo/ciclesonide) each of which lasted for one week and were separated by 3–5 weeks from the alternate treatment sequence. Patients received 800 μg ciclesonide twice daily by means of a Cyclohaler. At the end of each treatment patients were subjected to an allergen challenge.
Results: Thirteen asthmatic patients (mean FEV_1 of 91% predicted) who experienced an EAR and LAR after allergen challenge participated in the study. The time-average FEV_1 decreases 0–2 h (2–12 h) after allergen challenge as measure of the EAR (LAR) were significantly reduced ($P < 0.05$, one-sided) from 0.426 L to 0.233 L (EAR) and from 0.443 L to 0.213 L (LAR), respectively. Thus, the study results suggest that ciclesonide significantly lowered the extent of EAR and LAR compared to placebo. Ciclesonide was well tolerated and no drug-related adverse events were reported. Cortisol excretion in 24-h urine showed no significant difference between ciclesonide and placebo.
Conclusions: The study supports the efficacy and safety of ciclesonide.

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Key words: allergen challenge; asthma; early asthmatic reaction; inhaled steroids; late asthmatic reaction.

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Accepted for publication 10 August 2002

Asthma is defined clinically by reversible airway obstruction and bronchial hyperresponsiveness, and, pathologically, by chronic bronchial inflammation involving various cells and mediators (1). The role as primary controller therapy for inhaled corticosteroids (ICS) is widely accepted for treatment of asthma (1–4). However, not only do many patients express concerns about possible side-effects of inhaled corticosteroids (5,6) but the issue of efficacy *vs* safety remains of clinical importance (for a review see (7)).

Ciclesonide is a novel ICS under clinical development for the treatment of asthma. Ciclesonide itself is inactive and needs to be cleaved by esterases to bind to the glucocorticoid receptor (8). According to data from healthy volunteers, ciclesonide affected serum cortisol levels significantly less compared to beclomethasone dipropionate (8) suggesting that ciclesonide might have less systemic effects and hence a superior safety profile.

The current trial with ciclesonide is one of the first studies done in asthmatic patients. Its primary goal was to investigate whether ciclesonide is effective in man. For that purpose an allergen challenge was performed after one week of treatment to assess the effect of ciclesonide on early (EAR) and late allergic reactions (LAR).

Material and methods

Patients

Fifteen patients were enrolled in the study. Inclusion criteria were a history of wheezing episodes consistent with the clinical diagnosis of asthma, as defined by the American Thoracic Society (9). Otherwise, patients had to be in stable clinical condition and have a baseline FEV_1 of $>70\%$ predicted according to ECCS values (10). All patients demonstrated a positive prick test or radioallergosorbent assay (RAST) to one or more of the allergens tested (house dust mite, cat and dog hair, grass and birch pollen) and experienced both EAR and LAR after allergen challenge. None of the patients showed a history of relevant airway infection within 2 months prior to this study or was a heavy smoker defined as $=10$ cigarettes/day and $=10$ pack–years. All subjects only used short-acting bronchodilators on demand as rescue medication throughout the duration of the trial. The rescue medication had to be withheld for at least 8 h prior to each challenge.

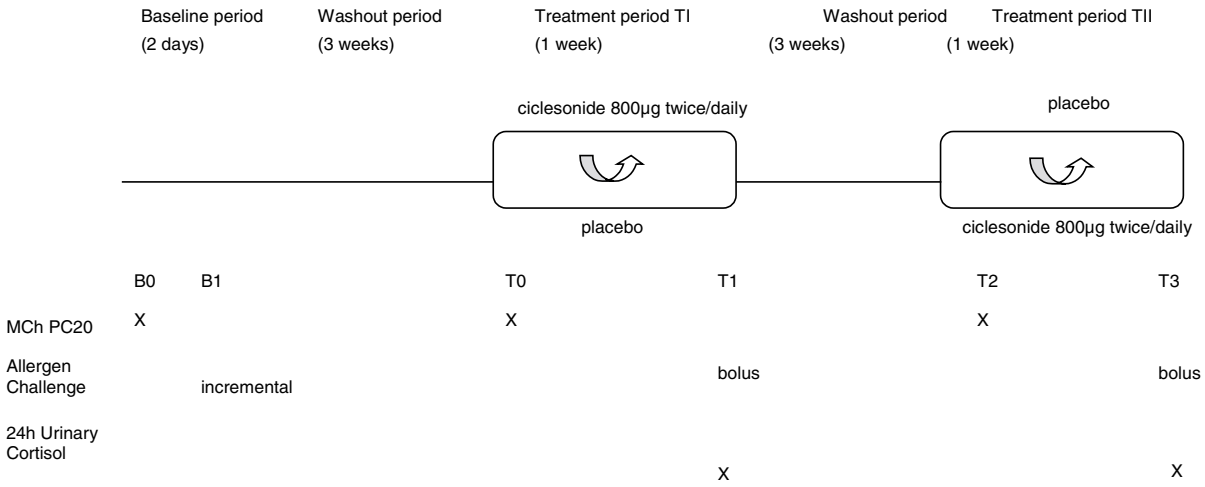

Figure 1. Design of the study.

Written informed consent was obtained from each patient prior to entering the trial. The protocol was approved by the Scientific Ethics Committee of Aarhus County and by the Danish Board of Health.

Study design

This trial was a randomized double-blind placebo-controlled cross-over study (Fig. 1). During baseline exclusion and inclusion criteria were verified and a methacholine and allergen challenge performed. After an interval of 3–5 weeks the patients were subjected to another methacholine challenge and entered the first treatment period TI, provided hyperreactivity to methacholine was within ± 2 concentration steps of PC_{20} FEV_1 value determined at visit B0. Patients were assigned randomly to a 1-week treatment period with either placebo or inhaled ciclesonide (800 µg twice daily), both supplied as powdered capsules and inhaled by means of a Cyclohaler (Novartis, Basel, Switzerland). Treatment period TII started after another washout period of at least 3 weeks in the manner described above. On the last day of each treatment period, an allergen challenge was performed 0.5 h after administration of the trial medication.

Measurements

At each visit a pulmonary function test was done with the best of three FEV_1 readings being used for analysis.

Methacholine challenge

After determination of baseline lung function, a bronchial challenge was performed using a standard Wright nebulizer (Wright & Filippis, Rochester Hills, MI, USA) calibrated to give a constant output of 0.13–0.15 ml/min. The patients inhaled methacholine as 2-min tidal breathing with a starting concentration of 0.03 mg/ml and subsequent doubling concentrations to a maximum of 32 mg/ml, until a drop of FEV_1, measured 90 s after each challenge, of at least 20% compared to saline occurred. PC_{20} was determined by interpolation.

Allergen challenge

The EAR and LAR were defined as a decrease in FEV_1 by at least 15% and 20%, respectively, referred to inhalation of the diluent. Allergen challenges for each individual patient were performed at the same time of day ± 30 min using a standard Wright nebulizer calibrated to give a constant output of 0.13–0.15 ml/min and patients were instructed to refrain from drinking caffeine-containing beverages and from smoking 4 h prior to each challenge.

Allergens used were grass and birch pollen, cat and dog hair, and house dust mite extracts (ALK-Abelló, Denmark). Before the challenge FEV_1 was measured followed by inhalation of the diluent (sodium chloride/albumin). If the diluent caused a fall in FEV_1 of $= 10\%$ compared to the baseline level the allergen challenge was deferred to another day. At baseline the allergen dose to be used during the treatment periods was determined by nebulizing the allergen continuously and exposing the patient to logarithmic concentrations of the individual allergen, as determined by skin prick and RAST tests.

Each patient started with a concentration equivalent to the one that gave a 3-mm wheal reaction during the skin prick test. Five and 10 min after two initial inhalations FEV_1 was measured, and if FEV_1 fell $<5\%$ compared to FEV_1 following diluent, the next concentration step was used. If the fall in FEV_1 was $> 5\%$ but $<15\%$, four inhalations with the same concentration were performed, followed by another eight inhalations if the fall in FEV_1 still did not exceed 15%. If the fall in FEV_1 remained at $> 5\%$ but $< 15\%$ the next concentration was used after a 10-min interval, applying the same requirements and conditions. The challenge was stopped if either the highest allergen dose had been inhaled or if FEV_1 had fallen by 15%. FEV_1 was measured at 5, 10, 15, 20, 30, 45, and 60 min and every hour between 2 h and 12 h thereafter.

The individually determined allergen dose that caused a LAR of FEV_1 of at least 20% was inhaled as a single dose at the end of both treatment periods. FEV_1 was recorded 5, 10, 15, 20, 30, 45, and 60 min afterwards and then in hourly intervals up to 12 h.

Safety assessments

Subjects were instructed to collect 24-h urine for determination of cortisol excretion starting the morning of the 6th treatment day and to return to the study site on day 7 (Fig. 1). Other safety aspects assessed at the end of each treatment period included monitoring of adverse events, routine clinical laboratory tests for hematology, biochemistry, urinalysis, a pregnancy test in females as well as a physical examination including resting ECG (12-lead).

Statistical analysis

As markers for the EAR and LAR the respective areas under the curve (AUC) (0–2 h) and (2–12 h) between the diluent reference value and the FEV_1 time course were determined and then divided by the duration of the respective periods (so-called time–averages). Comparison between treatments was done by the analysis of variance for the two-way, two-period crossover design. Mean and two-sided 90% confidence limits, corresponding to one-sided 95% confidence limits, were calculated for the difference ciclesonide–placebo of population means. The per-protocol analysis was done with 13 subjects. In addition, a subgroup analysis of 11 patients was performed since two of the 13 subjects did not experience a LAR during either of the two treatment periods.

A sample size of $n = 12$ patients had a power of 90% to detect for the above defined time-averages a difference in means in the order of one standard deviation, based on a paired *t*-test with a 5% one-sided significance level.

Results

Fifteen patients were recruited (Table 1). Two of them prematurely withdrew from the study (subject 8 due to lung function deterioration and subject 12 for nonmedical reasons); the other 13 successfully completed the study. Their mean FEV_1 at baseline amounted to 3.61 L corresponding to 91% predicted and they had an average PC_{20} FEV_1 of 3.29 mg/ml. FEV_1 values at the beginning of the two treatment periods were comparable as was the hyperresponsiveness to methacholine values suggesting that the washout period was long enough to prevent clinically relevant carry-over effects.

Efficacy

Mean FEV_1 values for the 13 subjects were 3.59 L at the beginning and 3.62 L at the end of the ciclesonide treatment and 3.56 L at the beginning and 3.58 L at the end of the placebo treatment. There were no significant differences within or between groups.

The allergen challenge results are summarized in Table 2 and Fig. 2. The time course in FEV_1 changes under placebo follows the typical time course in subjects showing a dual response (Fig. 2A). Compared to placebo ciclesonide significantly inhibited EAR from 0.426 L to 0.233 L ($P < 0.01129$, one-sided) and LAR from 0.443 L to 0.213 L ($P < 0.05$, one-sided). Furthermore, ciclesonide effectively reduced the maximum FEV_1 fall during both EAR and LAR by approximately 50%, with EAR – 26.9% for placebo *vs* – 12.6% for ciclesonide and LAR – 19.9% for placebo *vs* – 10.4% for ciclesonide.

Additionally, a subgroup analysis was done excluding the two subjects who did not experience a LAR during the placebo treatment period (subjects 4 and 15) (Fig. 2B). Differences between placebo and ciclesonide during the late-phase time-range become somewhat more pronounced, but basically the results were the same.

Safety

Eight subjects reported adverse events (headache, deterioration of asthma, upper respiratory tract infection) at some stage of the trial but none of the events occurred during the ciclesonide treatment period. With the exception of subject 8 who discontinued after placebo because of lung function deterioration, none of the patients prematurely left the study because of adverse events.

Cortisol excretion was evaluated by determining cortisol levels in 24-h urine at the end of each treatment period and adjusted by excretion of creatinine. No significant difference was found between cortisol/creatinine levels in the ciclesonide treatment group

Table 1. Demographic details of all cases at visit B0

			FEV_1				
Subject	Sex	Age (year)	L	% predicted	PC_{20} FEV_1 (mg/ml)	Challenge allergen	Smoking
1	F	19	4.13	104	>32	Grass	Never
2	M	22	4.60	103	6.5	HDM	Never
3	M	25	3.85	85	8.0	Cat	Never
4	F	21	3.15	88	0.3	Cat	Never
5	M	46	3.51	85	4.4	Birch	Never
6	M	36	4.08	93	>32	HDM	Never
7	F	24	3.69	105	2.8	HDM	Ex
8	M	20	4.70	100	6.6	HDM	10/day
9	F	37	3.44	103	6.0	Birch	Never
10	F	22	4.07	100	2.1	Cat	Never
11	M	44	3.08	84	2.2	Dog	Never
12	F	42	3.03	94	0.9	HDM	Ex
13	M	34	3.64	85	11.4	Grass	Ex
14	M	40	3.10	70	1.5	Cat	Never
15	F	25	2.61	82	0.1	Cat	10/day

PC_{20} FEV_1, concentration of methacholine to achieve a 20% fall in FEV_1.
HDM = house dust mite.

Table 2. FEV_1 (L) values after diluent and time-averaged FEV_1 decrements (L) after allergen challenge ($n = 13$)

Subject	Visit	Treatment	Diluent 5 min	0–2 h EAR	2–12 h LAR
1	T1	Ciclesonide	4.14	0.26	0.18
	T3	Placebo	4.00	0.35	0.20
2	T1	Placebo	4.53	0.73	0.51
	T3	Ciclesonide	4.77	0.23	−0.05
3	T1	Ciclesonide	4.32	0.17	0.19
	T3	Placebo	3.92	0.99	0.48
4	T1	Placebo	3.28	−0.07	0.01
	T3	Ciclesonide	3.69	0.32	0.29
5	T1	Placebo	3.40	0.24	0.44
	T3	Ciclesonide	3.26	0.07	0.09
6	T1	Ciclesonide	3.70	−0.17	−0.14
	T3	Placebo	3.88	0.08	0.26
7	T1	Placebo	3.56	0.50	1.04
	T3	Ciclesonide	3.64	0.28	0.33
9	T1	Ciclesonide	3.34	0.42	0.52
	T3	Placebo	3.24	0.62	0.68
10	T1	Placebo	4.01	0.84	0.41
	T3	Ciclesonide	4.27	0.32	0.77
11	T1	Placebo	2.72	0.09	0.32
	T3	Ciclesonide	3.14	0.16	−0.04
13	T1	Ciclesonide	3.46	0.35	0.34
	T3	Placebo	3.46	0.53	0.33
14	T1	Placebo	3.11	0.64	0.26
	T3	Ciclesonide	3.09	0.23	0.15
15	T1	Ciclesonide	2.59	0.39	0.16
	T3	Placebo	2.49	0.43	0.07

(15.49 nmol/mmol ± 5.37) and the placebo group (17.37 nmol/mmol ± 4.13).

In all subjects standard laboratory values were within normal ranges and there was no significant difference between pre- and post-treatment measurements.

Discussion

Patients were highly selected for this clinical experimental study. They all had mild allergic asthma and were currently not being treated with inhaled corticosteroids. To avoid an influence from tobacco smoking they were either nonsmokers or had less than 10 pack-years consumption. At inclusion they all had an early- and late-phase reaction following allergen challenge. The patients were selected with normal lung function. This is of importance for this type of study to avoid interference from airway geometry on measured responses. As baseline lung function remained stable during ciclesonide and placebo treatment periods, the responses after allergen challenge are due to inflammatory responses to allergen and a protective effect by the investigational drug, respectively.

The primary aim of this study was to assess the efficacy of inhaled ciclesonide *vs* placebo with respect to EAR and LAR after allergen challenge. It is well established that in asthmatic patients LAR improves after even a single dose of an ICS (11, 12) and that administration for about 1 week (however, not single dose (11, 13)) also attenuates the EAR (14–16). Our study demonstrates that 1600 μg ciclesonide/day given for one week significantly inhibits early- and late-phase allergic reaction and hence suggests that ciclesonide is effective in man. This is in agreement with results from another study which evaluated the effect of different doses of ciclesonide on airway hyperresponsiveness to adenosine-5′-monophosphate and on the number of eosinophils in sputum (17). Since the primary goal of our study was to prove the effectiveness of ciclesonide in man we chose a daily dosage of 1600 μg although lower doses probably would have been sufficient to suppress EAR and LAR. In fact the study by Swystun et al. (18) suggests that 200 μg budesonide/day given for one week are sufficient to inhibit the EAR with no further improvement seen after administration of 400 and 800 μg budesonide/day.

Inhaled corticoteroids, together with avoidance of trigger factors and use of rescue bronchodilators, remain the first-choice therapeutic option for the management of bronchial asthma. However, in recent years some ICS have undergone a class relabeling approved in the US (19, 20), and the British Committee on Safety of Medicines (21) has also emphasized some warnings. In general, careful safety evaluation of patients, especially those taking high doses for long periods and pediatric patients, is required. Thus, there is a need for newer generation ICS with improved safety profiles.

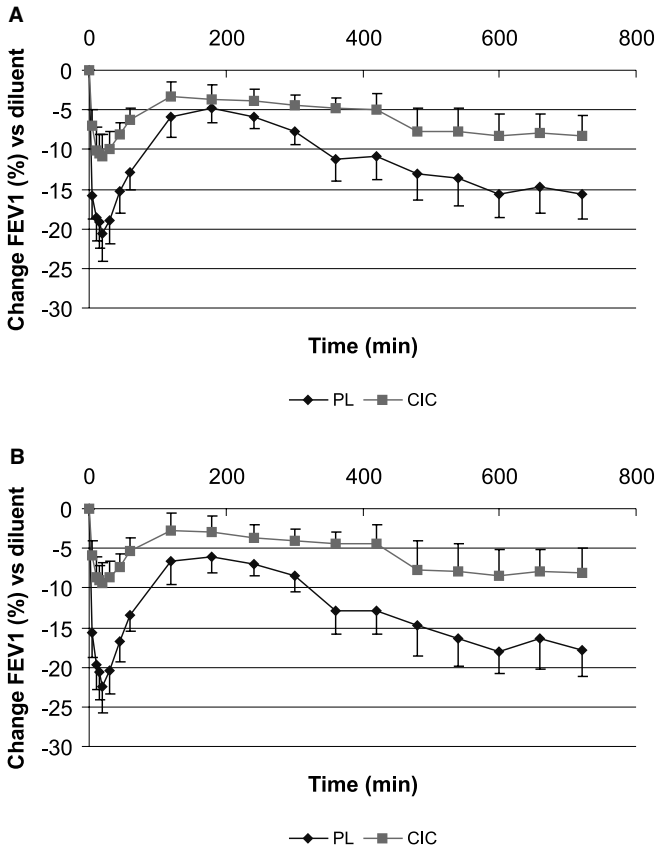

Figure 2. FEV1 time-course (± SEM) after allergen challenge following treatment with either ciclesonide (CIC) or placebo (PL). A, $n = 13$; B, $n = 11$.

In studies with ICS, effects on cortisol secretion are being determined not only to assess any relevant interference with HPA axis in individuals but also to study the overall potential for systemic effects of ICS in general, using cortisol as a marker. Therefore, in the current trial 24-h urinary cortisol was determined to assess the systemic effects of ciclesonide. No significant difference to placebo was found. This is in line with the results of a study in healthy volunteers where the 24-h mean levels for serum cortisol under ciclesonide 800 μg given either in the morning or in the evening for 1 week was 2–6% lower compared to placebo indicating that ciclesonide lacks relevant systemic effects (22). It should be noted that in the latter study ciclesonide was given by metered-dose inhaler (MDI) which has a considerably higher respirat-able fraction (data on file at Byk Gulden) compared to the powder formulation (respirable fraction 21–32%) used in the current study.

In summary, the study presented here strongly suggests that ciclesonide is effective in patients with mild asthma with regards to allergic airway hyperresponsiveness, without evoking adverse events, and thus may be an alternative to existing ICS.

Acknowledgments

The conduct of the study was supported by a grant from Byk Gulden Pharmaceuticals.

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