ERJ Express. Published on January 22, 2009 as doi: 10.1183/09031936.00079908

EFFECTS OF CICLESONIDE AND FLUTICASONE ON CORTISOL SECRETION IN PATIENTS WITH PERSISTENT ASTHMA

[1]Eric Derom, [2]Renaud Louis, [3]Christine Tiesler, [3]Renate Engelstätter, [4]Jean-Marc Kaufman, and [1]Guy. F. Joos

[1]Department of Respiratory Medicine, Ghent University Hospital, Belgium; [2]Department of Respiratory Diseases, Université de Liège, Belgium; [3]Nycomed Pharma, Konstanz, Germany; and [4]Department of Endocrinology, Ghent University Hospital, Belgium.

Address for correspondence:

Eric Derom

Department of Respiratory Medicine
Ghent University Hospital

De Pintelaan 185
B-9000 Ghent
Belgium

Tel: 32-9-3322359
Fax: 32-9-3322341
E-mail: eric.derom@Ugent.be

Running head: Systemic effects of ciclesonide and fluticasone

Word count: 4546

ABSTRACT

We compared the systemic and clinical effects of ciclesonide (CIC) and fluticasone propionate (FP), given on top of CIC 160 µg/day and salmeterol 50 µg twice daily in 32 patients with persistent asthma using a randomized double-blind, placebo-controlled, double-dummy, five-period crossover design.

All patients exhibited a PC_{20} methacholine <8 mg/ml and a PC_{20} adenosine <60 mg/ml. Primary outcome was 24-h serum cortisol suppression after seven days. Secondary outcomes were changes in PC_{20} methacholine and adenosine after 9 days.

FP 500 µg/day and 1000 µg/day significantly suppressed cortisol secretion versus placebo by –46.2 (95%C.I.: –83.8,–8.5) nmol/L and by –76.1 (95%C.I.: –112.9,–39.3) nmol/L, respectively. Neither dose of CIC (320 or 640 µg/day) had a significant suppressive effect [–28.2 (95%C.I.: –65.5,+9.2) nmol/L and – 37.3 (95%C.I.: –74.7, 0.0) nmol/L, respectively]; differences between FP 1000 µg/day and both CIC treatments were statistically significant [for CIC 320 µg/day: –48.0 (95%C.I.: –84.8,–11.1) nmol/L; for CIC 640 µg/day: –38.8 (95%C.I.: –75.7,–1.9) nmol/L]. Compared with placebo, the increase in PC_{20} adenosine after the four treatments was small, but significant. Greater improvements in PC_{20} adenosine were seen with FP 500 µg/day [1.8 (95%C.I.: 1.0, 2.6) doubling concentrations] compared with CIC 320 µg/day [0.9 (95%C.I.: 0.1, 1.7) doubling concentrations]; no significant difference was seen between CIC 640 µg/day and FP 1000 µg/day.

For a similar decrease in hyperresponsiveness, cortisol secretion was suppressed significantly with moderate to high doses of FP, but not with CIC.

Key words: aerosol therapy, anti-asthmatic agent, asthma, bronchial hyperreactivity, inhaled corticosteroids, cortisol

INTRODUCTION

Inhaled corticosteroids (ICS) are the most effective controller medications currently available to treat asthma. They reduce airway inflammation and hyperresponsiveness, improve symptoms, pulmonary function and quality of life [1,2] and decrease hospitalizations [3] and mortality rate [4]. ICS are thus the guideline-recommended first-line treatment for all patients with persistent forms of the disease [5]. Although the vital role of ICS in the management of asthma is generally recognized and ICS are well tolerated at low-to-medium doses, it has been claimed that the long-term administration of high doses of ICS has a potential for systemic adverse events (AEs), such as growth inhibition, osteoporosis, suppression of hypothalamic–pituitary–adrenal (HPA)-axis function [6] or even adrenal crisis [7]. This potential for AEs with ICS is a concern for patients and physicians, and may contribute to intentional nonadherence [8] and sub-optimal prescribing [9].

Ciclesonide (CIC) is a novel, airways-targeted ICS that is delivered as an inactive compound and converted by esterases to the active metabolite (desisobutyryl-ciclesonide) in the airways, where it elicits its anti-asthmatic effect [10-13]. Several trials have shown that doses up to 1280 μg/day of CIC do not produce clinically relevant HPA-axis suppression in both healthy volunteers and asthma patients [13-18]. Fluticasone propionate (FP) is an established ICS, which has, however, been associated with pronounced suppression of HPA-axis function in healthy volunteers [19] and to a lesser extent, in asthma patients [14,15,20-22]. The current study was thus designed to assess the safety of CIC and FP in patients with persistent asthma chronically treated with ICS. More specifically, we wanted to address: 1) whether moderate-to-high doses of inhaled CIC suppress 24-h serum and urinary cortisol levels and biochemical markers of bone formation in patients with moderate persistent asthma and how these effects compare with those of moderate-to-high doses of FP; 2) to what extent do moderate-to-high doses of CIC reduce airway responsiveness to adenosine and methacholine, and how these effects compare with those of moderate-to-high doses of FP; and 3) whether one of the two investigated formulations is superior in terms of the ratio between clinical effect and systemic effect.

METHODS

Patients

Male and female patients (aged 18−65 years) known to have persistent asthma for more than 6 months, as defined by the Global Initiative for Asthma GINA, were allowed to participate in the study. Patients were included if their current treatment consisted of a constant dose of a moderate to high daily dosage of ICS alone (beclomethasone dipropionate ≤1000 µg/day or equivalent) or a combination of low doses of ICS with long-acting $ß_2$-agonists (LABA) (beclomethasone 200 µg twice daily [bid] or equivalent plus salmeterol 50 µg bid or formoterol ≤12 µg bid) for more than 4 weeks. Patients with severe persistent asthma were excluded to avoid drop-outs. Patients had to demonstrate a FEV_1 of >60% predicted at the study start and at randomization. They all exhibited a PC_{20} methacholine (provocative concentration of inhaled methacholine leading to a 20% decrease in post-saline FEV_1) <8 mg/mL) and a PC_{20} adenosine (provocative concentration of adenosine leading to a 20% decrease in post-saline FEV_1) <60 mg/mL. Patients were also required to have normal HPA-axis function (serum cortisol concentration at 8.00 am [± 30 minutes] >5 µg/dL [>138 nmol/L]) and not to have experienced an asthma exacerbation or respiratory tract infection within 8 weeks prior to the start of the study.

Patients were excluded if they had used systemic steroids within 4 weeks of study start or more than three times during the last 6 months; had chronic obstructive pulmonary disease and/or other pulmonary diseases; had a history of other medical conditions known to affect cortisol levels (e.g. Cushing's Syndrome); or were receiving drugs known to affect endogenous cortisol production (e.g. anabolic steroids or androgens). Females were excluded if they were pregnant, giving breast feeding or not using safe contraception, were of childbearing potential, or were <1 year postmenopausal.

This study was conducted in accordance with the rules of the International Conference on Harmonization Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Written consent was obtained from the patients before the start of the study, and the protocol was reviewed and approved by the appropriate Independent Ethics Committee or Institutional Review Boards.

Study design

This randomized, double-blind, double-dummy, placebo-controlled, five–period crossover study was conducted at two centers in Belgium (Fig. 1). During a 4–6 week run-in period, patients were administered CIC 160 µg in the evening plus salmeterol 50 µg bid. This treatment was continued throughout the entire study. Ciclesonide was chosen because studies have previously shown that daily doses of up to 1280 µg CIC had no clinically relevant effect on cortisol secretion [14,16,17]. Following the run-in period, patients were randomly assigned to one of ten treatment sequences, occurring in a Latin square and its mirror, for which a computer generated randomization list was used (Table 1). These ten sequences were uniform on the periods (each treatment was applied with the same frequency in each period) and on the subjects (each treatment was applied with the same frequency within each subject), and balanced with respect to a first order carry-over effect (each treatment preceded every other treatment a same number of times).

Each treatment sequence consisted of five-period treatments which contained one of the following study medications (all administered via hydrofluoroalkane metered dose inhaler

[HFA]–MDI) given on top of the CIC 160 µg/day maintenance dose: CIC 160 µg bid (ex-actuator); CIC 320 µg bid (ex-actuator); FP 250 µg bid (ex-valve; 220 µg bid ex-actuator); FP 500 µg bid (ex-valve; 440 µg bid ex-actuator); or placebo. Due to the code labeling, neither the investigator nor anyone at the study center knew which drug or dosage was administered. The FP doses were based on previous observations, showing equivalence of CIC 320 µg/day with FP 500 µg/day in terms of bronchial responsiveness to methacholine [15,23]. The study medication was inhaled at 8:00 am and 8:00 pm (± 30 min), starting at the evening of each period. The last inhalation took place 30–60 min before the methacholine provocation on the ninth day of treatment. Each treatment period was separated by a 4–12-week washout period, to allow for all previously administered study drug to be cleared from the system and to allow PC_{20} adenosine [14] and serum cortisol [20,24] to return to baseline values.

Spirometry and measurement of airway hyperresponsiveness

Spirometry was performed at study start (between 8.00–10.00 am) and repeated at the beginning and end of each 9-day treatment period at approximately the same time point. The highest value from three acceptable tests was recorded for FEV_1. Rescue medication had to be withheld for ≥8 h and LABAs for ≥24 h prior to each lung function measurement.

Challenge tests were performed at the study start and at the end of each treatment period (visits T2, T5, T8, T11 and T14; Fig. 1) 30–60 min after the last dose of study medication, according to a protocol that has been described previously [14,25]. Methacholine solutions were nebulized with a Wiesbadener Doppel inhalator, driven at an airflow of 6 L/min, generating an output of 0.1 mL per min [25]. Median mass particle size of the aerosol was 3.5 µm. Each patient used the same nebulizer for the whole study. The aerosol was inhaled during 2 min of quiet breathing with the outlet of the nebulizer in the mouth and the nose occluded with a clip. Three baseline readings were followed by inhalation of aerosolized saline. If

FEV_1 had not fallen by more than 10%, aerosolized methacholine was administered, the initial concentration being 0.031 mg/mL. Its concentration was doubled after each step. Spirometric measurements were performed 1 and 3 min after each concentration; the lowest out of these two was retained for analysis. The time interval between each step was 5 min. The procedure was terminated once FEV_1 had decreased by at least 20% or when the maximum methacholine concentration (32 mg/mL) had been reached. The PC_{20} methacholine was calculated via linear interpolation on a logarithmic dose–response curve. If the FEV_1 had not fallen by 20% or more at the maximum methacholine concentration of 32 mg/ml, that value was substituted by 64 mg/mL.

Following methacholine challenge, the patient was allowed to recover for 2–4 h (without use of rescue medication). If FEV_1 had returned to > 90% of the pre-challenge value, an adenosine challenge was performed in the same manner as detailed above (doubling concentrations ranging from 1.563–410 mg/mL diluted in 0.9% saline) and PC_{20} was recorded. If the FEV_1 had not fallen by 20% or more at the maximum adenosine concentration of 410 mg/ml, that value was substituted by 820 mg/mL. Patients unable to complete an adenosine challenge on the same day as the methacholine challenge returned on the following day.

Cortisol assessments

Twenty-four hour serum profiles were obtained from all patients after 7 days of each treatment (visits T1, T4, T7, T10 and T13 [Fig. 1]). At these visits, patients stayed at the study site for 24 hours and 5 mL of blood was drawn at 2-h intervals starting at 8.00 pm (±10 min) until 8.00 pm (±10 min) the following day. Urine was collected over 24 h at the same visits. Creatinine was also measured in the samples.

Bioanalytical methods

Blood samples for cortisol analysis were collected in tubes without anticoagulant. After collection the tubes were mixed gently and incubated for a minimum of 10 min and a maximum of 2 hours before centrifugation for 15 min at 3000 rpm at room temperature. The serum was then transferred to new tubes and stored at –20°C until analysis. Urine was collected for about 24 h, the total volume recorded and one teaspoon of sodium-azide per 2.5 L container added as a preservative. Well-mixed aliquots were stored at –20°C. Serum and urinary cortisol were measured using the GammaCoat (I^{125}) Cortisol Radioimmunoassay Kit procedure of Diasorin, which is based on the competitive binding principles of radioimmunoassay; urine was extracted before radioimmunoassay of cortisol after addition of a titrated cortisol internal standard for recovery monitoring. The limit of quantification was 0.5 µg/dL with an intra-batch coefficient of variation of 3% and an inter-batch coefficient of variation between 5.5–7.1%. For a given patient, all samples were assayed for cortisol within the same assay run. Possible interference of the trial medication with the cortisol assay antibody was assessed and no interference was found. Urinary creatinine was measured according to Jaffe (kinetic colorimetric assay) using a Roche/Hitachi MODULAR analyzer.

Assessment of bone formation makers

Blood samples to determine serum biochemical markers of bone formation were obtained on the second day of Visits T1, T4, T7, T10 and T13 at 8.00 am (±10 min) after 8 h of fasting. All samples from a given patient were assayed in a single assay run using commercial immunoassays for bone alkaline phosphatase (AP; ACCESS Immunoassay Systems, Beckman Coulter Inc, Galway, Ireland), serum osteocalcin (N-MID Osteocalcin; Osteometer Biotech A/S Copenhagen, Denmark) and serum N-terminal propeptide of type 1 procollagen (P_1NP; Orion Diagnostica, Espoo, Finland).

Adverse events

Safety was assessed throughout the study by neutral questioning.

Statistical analysis

The primary variable was the 24-h serum cortisol mesor, calculated by means of the area under the curve of the 24-h serum cortisol profile ($AUC_{0–24h}$) divided by the respective time interval (8.00 pm until 8.00 pm of the following day) using the trapezoidal rule. Replacement of missing values or of outliers was not performed. A second important variable was 24-h free urine cortisol adjusted for creatinine.

To address the multiplicity issue, a strategy with a priori ordered hypotheses was applied which preserves the familywise error of the procedure at $\alpha=0.025$ (one-side). Consequently, superiority hypotheses for 24-h serum cortisol mesor and 24-h free urine cortisol adjusted for creatinine were one-sided at a significance of $\alpha=0.025$. Only if the previous null hypothesis could be rejected, the subsequent superiority test would be carried out in the following order: superiority of CIC 640 µg/day to FP 1000 µg/day for difference in serum cortisol mesor; superiority of CIC 640 µg/day to FP 1000 µg/day for change in 24-h urine cortisol adjusted for creatinine; superiority of CIC 320 µg/day to FP 500 µg/day for difference in serum cortisol mesor; superiority of CIC 320 µg/day to FP 1000 µg/day for change in 24-h urine cortisol adjusted for creatinine.

All statistical analyses were carried out with SAS (release 9.1). Serum cortisol mesor, urine cortisol variables, bone formation markers, log-transformed PC_{20} and lung variables were analyzed by means of an analysis of covariance or an analysis of variance [26] with treatment, period, sequence, patient within sequence, and gender as factors. For computation of the ANOVA and ANCOVA analyses the SAS procedure PROC MIXED was utilized, using the baseline value as continuous covariate, the patient within sequence effect as random nested factor and all other factors as fixed effects. Asthma pre-treatment and centre as factors were added for specific endpoints or analyses. T-tests of difference between the treatment least square means are given as two-sided, with an α level of 5%. The sample size was estimated based on findings from a previous study [14]. In the case of normally distributed difference in time-averaged cortisol levels AUC_{0-24h}, a sample size of 30 randomized patients was estimated to ensure a power of 80% to correctly conclude a difference in mean values of 49 nmol/L under assumption of a common standard deviation of 66.6 nmol/L. The sample size estimation was based on a two-independent-group *t*-test which provides a conservative acceptable approximation of the t-test for comparing least-square means utilized in the PROC MIXED procedure.

RESULTS

Patient characteristics

A total of 83 patients were screened. Of these, 51 were not eligible because of a negative methacholine or negative adenosine challenge test. The remaining 32 patients (20 females) were randomized (Table 2. Fig. 2). The first patient was included on May 27th 2003 and the last patient left the study on April 10th 2006. The characteristics of the 32 patients included in the study are summarized in Table 2. Median age was 27 years. Most patients were pretreated with a combination of a LABA and an ICS. Mean PC_{20} methacholine was 2.0 mg/mL and mean PC_{20} adenosine was 16.7 mg/mL. Washout period was 4 weeks on most occasions, and did not exceed 8 weeks. There were no dropouts due to asthma exacerbations. Two patients ended the study prematurely for non medical reasons and were excluded from the safety analysis. One further patient was excluded from all analysis for erroneously using his previous ICS (FP Diskus) during the study.

Cortisol assessments

Serum cortisol mesor

Data are presented in Table 3. Both FP doses significantly suppressed cortisol secretion versus placebo, serum cortisol reaching 323.0 ± 22.6 nmol/L after FP 500 µg/day [–46.2 (95% C.I.: –83.8, –8.5) nmol/L or –10.3%] and 293.0 ± 22.3 nmol/L after FP 1000 µg/day [– 76.1 (95% C.I.: – 112.9,– 39.3) nmol/L or –19.8%]. Differences in supression between FP 1000 µg/day and both the CIC 320 µg/day [–48.0 (95% C.I.: –11.1,–84.8) nmol/L] and CIC 640 µg/day [–38.8 (95% C.I.: –1.9,–75.7) nmol/L] treatments also reached statistical significance. Neither dose of CIC had a significant suppressive effect (Table 3; Fig. 3).

24-h urine cortisol adjusted for creatinine

Data are presented in Table 3. Urinary cortisol excretion over 24 h adjusted for creatinine was significantly suppressed by both FP doses as compared with placebo. Neither dose of CIC demonstrated a significant effect on 24-h urinary cortisol adjusted for creatinine compared with placebo.

Assessments of bone formation makers

No significant differences were noted after either CIC treatment compared with placebo for any bone formation marker assessed (Table 4). However, FP 1000 µg/day caused significant decreases in P_1NP (p=0.0126) and serum osteocalcin levels (p=0.0054) compared with placebo (Table 4).

Pulmonary function measures

FEV_1 remained stable over time, 90 mL being the largest difference between the highest and the lowest value. Changes from baseline in FEV_1 % predicted (least square means) were small for all treatments (CIC 320 µg/day, –0.2%; CIC 640 µg/day, –0.3%; FP 500 µg/day, 1.4%; FP 1000 µg/day, 3.3%; placebo, –3.1%).

Methacholine and adenosine 5-monophosphate challenge

Mean PC_{20} methacholine, which was 2.0 mg/mL at inclusion increased during the study by one doubling concentration (DC), reaching 5.6 mg/mL under placebo conditions. Placebo here means that patients remained under an evening dose of CIC 160 µg throughout the study. Further improvements in airway hyperresponsiveness with the active treatments were small compared with placebo and were less than one DC (Fig. 4 – Table 5). PC_{20} methacholine after the two FP treatments thus increased by 0.6 and 0.7 DC compared with placebo ($p \leq 0.0228$), whereas the changes in hyperresponsiveness (0.3 and 0.5 DC) after CIC did not reach statistical significance (Table 5). Statistically significant differences between the CIC and FP treatments for PC_{20} methacholine challenge were not observed.

Mean PC_{20} adenosine, which was 16.7 mg/mL at inclusion, increased during the study by almost two DC, reaching 51.3 mg/mL under placebo conditions. The further increase in PC_{20} adenosine with all four treatments was statistically significant compared with placebo, ranging between 1 and 2 DC ($p<0.05$; Fig. 5; Table 5). Differences between the lower and the higher dose of CIC did not reach statistical significance. Likewise, the differences between the two FP doses were not statistically significant. FP 500 µg/day resulted in significantly greater improvements in PC_{20} adenosine (one DC) compared with CIC 320 µg/day ($p=0.0238$); no significant difference was seen between CIC 640 µg/day and FP 1000 µg/day, or between other doses.

Safety

In total, 22 patients experienced 56 AEs during the treatment period. The percentage of patients experiencing AEs was comparable across all treatment groups (CIC 320 μg/day, 33.3%; CIC 640 μg/day, 26.7%; FP 500 μg/day, 31.3%; FP 1000 μg/day, 22.6%; placebo, 33.3%). The majority of AEs were mild or moderate in intensity and none were assessed as definitely related to study medication. One patient in the placebo group reported two serious AEs (face edema; laryngeal edema), which were due to allergy to concomitant use of antibiotics and resolved completely.

DISCUSSION

The present study is the first placebo-controlled, crossover study assessing simultaneously the effects of ICS on cortisol secretion, bone markers and bronchial hyperresponsiveness in ICS-dependent asthma patients. The results indicate that daily doses of CIC 320 and 640 μg, given on top of a low maintenance dose of CIC 160 μg/day, did not appear to exert significant systemic effects, whereas daily doses of FP 500 and 1000 μg significantly suppressed adrenal function and bone formation markers. All active treatments improved airway responsiveness, but clinically relevant differences between the treatments were not observed.

The magnitude of the suppression of serum cortisol mesor, the primary variable, reached 10% with FP 500 μg/day and almost 20% with FP 1000 μg/day, given on top of a low maintenance dose of CIC 160 μg/day. Likewise, 24-h urinary cortisol excretion (adjusted for creatinine) was lower with FP than with placebo treatment. Substantial suppression of adrenal function after inhalation of FP has been previously reported in healthy volunteers [19] and asthmatic patients [14,20-22]. The presently observed degree of adrenal suppression with FP 1000 μg/day is somewhat smaller than the 29–34% suppression, reported previously [14,17,20], possibly because it was given on top of a low maintenance dose of inhaled CIC. The duration of the treatment cannot explain the difference between the currently and previously reported decreases in suppression, as adrenal suppression with inhaled FP is close to maximum after 7 days [27]. Possibly, the alterations in pulmonary function and airway inflammation in patients with more severe asthma resulted in a less distal lung deposition of FP, leading to a reduced pulmonary absorption, a decreased systemic bioavailability and a less pronounced adrenal suppression [22,28-30].

In contrast to FP, CIC 320 and 640 μg/day, even given on top of a low maintenance dose of CIC 160 μg/day, did not significantly alter cortisol production. Indeed, mean change in serum cortisol was –6.1% for CIC 320 μg/day and –7.9% for CIC 640 μg/day, which is in complete agreement with changes reported in previous studies [14,17]. An important finding was that differences in serum cortisol mesor between FP 1000 μg/day and the two CIC treatments reached statistical significance. Similar observations have been reported in other studies, in which the systemic effects of CIC and FP in healthy volunteers or patients with mild asthma have been assessed [14-17], be it at higher doses. It thus appears that the effects on the 24-h cortisol profile induced by FP are an intrinsic characteristic of this molecule and occur in both healthy subjects and patients with intermittent and persistent asthma. Interestingly, such effects have not been reported with CIC, even in doses as high as 1280 μg/day [14,17].

Differences in pharmacokinetic properties between FP and CIC may largely explain the more beneficial profile of CIC [31,32]. Although the clinical relevance and long-term consequences of mild adrenal suppression remain to be elucidated, the potential clinical relevance of this finding should not be underestimated. Moreover, the wide confidence intervals for serum cortisol for all comparisons indicate that the individual variability of the response of the HPA-axis and the potential occurrence of measurable systemic effects towards different doses of different inhaled steroids cannot be neglected. Indeed, a substantial number of patients with moderate or severe asthma are treated with high doses of FP, i.e. 1000 μg/day or more, in order to reach asthma control [5,33].

Admittedly, a carry-over effect could have been missed, since this study was powered for the primary outcome. It is, however, unlikely that such a carry-over effect may have occurred, since des-ciclesonide has a half-life of just over three hours [32] and fluticasone has a half-life between 7 and 14 hours [31], whereas washout in the present study was at least 4 weeks. Moreover, cortisol secretion recovers completely 24 h after a single inhalation of 1000 μg fluticasone [24], while PC_{20} adenosine normalizes completely 4 weeks after discontinuation of a treatment with inhaled steroids [14,34].

Looking at markers of bone metabolism is a different way of assessing systemic effects of ICS. The current study suggests that FP 1000 μg/day significantly decreased P_1NP and serum osteocalcin, whereas the lower dose of FP and both doses of ICS did not. Long-term studies with FP, in which doses from 400–750 μg/day were administered for 1–2 years demonstrated no clinically relevant effect on markers of bone formation compared with baseline [35,36]. To the best of our knowledge, no studies with higher doses of FP have been performed to date. The clinical relevance of our findings remains to be determined, although some evidence exists that long-term ICS use affects bone mineral density and increases the risk of fractures [6].

The secondary endpoints of the present study compared the clinical effects of the different treatments with those seen with placebo. Although FEV_1 is often used as a marker for the clinical effect of anti-asthma drugs, this test cannot be used to establish the relative potency of ICS [14,20]. This is confirmed in the present trial, the observed differences in FEV_1 between active and placebo treatments being very small. However, it has been suggested that challenges tests with methacholine [37] and adenosine [38] might be more appropriate to differentiate the effects of high and low doses of ICS. In previous studies, CIC, inhaled via dry powder inhaler, has demonstrated dose-dependent improvements in adenosine challenge up to doses of 1280 µg/day [14,38], and significant protective effects versus placebo at doses as low as 160 µg/day may be expected [12]. Likewise, dose-dependent protective effects of FP against adenosine and methacholine challenge have been documented in previous studies [39].

With regard to the current study, the overall effects of the ICS on bronchial hyperresponsiveness against methacholine were small, the observed changes ranging between 0.3 and 0.7 DC. This is in keeping with previously published data [15,23,39]. In the present study, in which FP and CIC were inhaled on top of a low maintenance dose of CIC, only the improvement by 0.6 and 0.7 DC with the two doses of FP reached statistical significance, a finding of little clinical relevance. These small increases did not allow us to establish the relative potency of the four treatments. Possibly, greater and more discriminative effects could have been obtained by prolonging each treatment to 52 weeks, a time point at which the maximum effects of ICS on PC_{20} methacholine may be expected [40].

Adenosine-induced bronchoconstriction has been shown to be sensitive marker of airway inflammation by promoting the release of a variety of inflammatory mediators [41], correlates with both exhaled NO and sputum, blood and bronchial tissue eosinophilia [42] and appears to be better suited to assess the anti-inflammatory effects of ICS than methacholine [43,44]. In the present study, the room for improvement in PC_{20} with both CIC and FP was larger with adenosine than with methacholine, a finding that is in line with a study in which a high dose of ICS increased PC_{20} adenosine by 3.1 DC and PC_{20} methacholine only by 1.5 DC [43]. Nevertheless, the absolute increases in PC_{20} adenosine with FP and CIC observed in the present study did not exceed two DC, when compared with placebo. This contrasts with previous data by Philips [45] for FP and by Taylor and Kanniess [38,46] for CIC. CIC 400 μg/day, administered via dry powder inhaler for 14 days, thus increased PC_{20} adenosine by 2.0 DC and 2.4 DC and 1600 μg/day increased PC_{20} adenosine by 3.4 DC [38,46]. In a study with FP 1000 μg/day, PC_{20} adenosine increased by approximately 4.5 DD [45].

Differences in methodology may largely explain the observed between study differences in magnitude of effect. Firstly, the maximum treatment period of 10–12 days chosen to avoid an overall study duration in excess of 6 months, may have limited the increase in PC_{20} adenosine, which requires up to 4 weeks to reach a maximum [37,45,47]. Moreover, the administration of a maintenance dose of CIC 160 μg/day to preserve asthma control may have contributed to the unexpected, more than twofold increase in PC_{20} adenosine, compared with PC_{20} values obtained at inclusion. Possibly, the inclusion into the study improved adherence to treatment, which in daily life is known to be less than optimal in many asthma patients. This unexpected rise in DC limited the room for further improvements in PC_{20} adenosine with any of the active treatments. As the overall improvements in bronchoprotection against adenosine were small (only the difference between CIC 320 μg/day and FP 500 μg/day reached statistical significance), the relative potencies of the different treatments could not be established.

In summary, results from the current study indicate that FP 500 and 1000 μg/day exerted systemic effects in patients with moderate persistent asthma, whereas CIC 320 or 640 μg/day did not affect either biochemical markers of bone formation or serum and urinary cortisol values, if given on top of a low ciclesonide dose. Although the long-term clinical meaning of these markers remains to be investigated, they do suggest that CIC yields less systemic effects than FP in patients with moderate persistent asthma for a similar protective activity. The importance of this issue cannot be overestimated in the light of the currently accepted aims of asthma treatment [5], in which disease control with higher doses of ICS features as the primary objective.

ACKNOWLEDGEMENTS

This study was funded by Nycomed. It is a pleasure to acknowledge the late Prof. Romain Pauwels for his contribution to the design of the study, Jochen Dunkel for statistical advice, and Mrs. Vera Collart, Mrs. J. Sele, Mrs. Greet Van Severen and Mr. Sven Verschraegen for excellent technical assistance. The authors would also like to thank Andrew Owen, MSc, Medicus International, for his editorial assistance.

REFERENCES

1. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med* 1998;157:S1-S53.

2. Banov C, Howland WC, III, Lumry WR, Parasuraman B, Uryniak T, Liljas B. Budesonide turbuhaler delivered once daily improves health-related quality of life in adult patients with non-steroid-dependent asthma. *Allergy Asthma Proc* 2003;24:129-136.

3. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;57:880-884.

4. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-336.

5. O'Byrne P, GINA scientific committee, GINA executive Committee. Global Initiative for asthma. Global strategy for asthma management and prevention. 2006.

6. Kelly HW. Potential adverse effects of the inhaled corticosteroids. *J Allergy Clin Immunol* 2003;112:469-478.

7. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;87:457-461.

8. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am* 2005;25:107-130.

9. Adams RJ, Fuhlbrigge A, Guilbert T, Lozano P, Martinez F. Inadequate use of asthma medication in the United States: results of the asthma in America national population survey. *J Allergy Clin Immunol* 2002;110:58-64.

10. Mutch E, Nave R, McCracken N, Zech K, Williams FM. The role of esterases in the metabolism of ciclesonide to desisobutyryl-ciclesonide in human tissue. *Biochem Pharmacol* 2007;73:1657-1664.

11. Pearlman DS, Berger WE, Kerwin E, Laforce C, Kundu S, Banerji D. Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2005;116:1206-1212.

12. Wilson AM, Duong M, Pratt B, Dolovich M, O'Byrne PM. Anti-inflammatory effects of once daily low dose inhaled ciclesonide in mild to moderate asthmatic patients. *Allergy* 2006;61:537-542.

13. Langdon CG, Adler M, Mehra S, Alexander M, Drollmann A. Once-daily ciclesonide 80 or 320 microg for 12 weeks is safe and effective in patients with persistent asthma. *Respir Med* 2005;99:1275-1285.

14. Derom E, Van De Velde V, Marissens S, Engelstätter R, Vincken W, Pauwels R. Effects of inhaled ciclesonide and fluticasone propionate on cortisol secretion and airway responsiveness to adenosine 5'monophosphate in asthmatic patients. *Pulm Pharmacol Ther* 2005;18:328-336.

15. Lee DK, Fardon TC, Bates CE, Haggart K, McFarlane LC, Lipworth BJ. Airway and systemic effects of hydrofluoroalkane formulations of high-dose ciclesonide and fluticasone in moderate persistent asthma. *Chest* 2005;127:851-860.

16. Lipworth BJ, Kaliner MA, LaForce CF, Baker JW, Kaiser HB, Amin D, Kundu S, Williams JE, Engelstätter R, Banerji DD. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol* 2005;94:465-472.

17. Szefler S, Rohatagi S, Williams J, Lloyd M, Kundu S, Banerji D. Ciclesonide, a novel inhaled steroid, does not affect hypothalamic-pituitary-adrenal axis function in patients with moderate-to-severe persistent asthma. *Chest* 2005;128:1104-1114.

18. Weinbrenner A, Huneke D, Zschiesche M, Engel G, Timmer W, Steinijans VW, Bethke T, Wurst W, Drollmann A, Kaatz HJ, Siegmund W. Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide. *J Clin Endocrinol Metab* 2002;87:2160-2163.

19. Lönnebo A, Grahnén A, Jansson B, Brundin RM, Ling-Andersson A, Eckernas SA. An assessment of the systemic effects of single and repeated doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers. *Eur J Clin Pharmacol* 1996;49:459-463.

20. Derom E, Van Schoor J, Verhaeghe W, Vincken W, Pauwels R. Systemic effects of inhaled fluticasone propionate and budesonide in adult patients with asthma. *Am J Respir Crit Care Med* 1999;160:157-161.

21. Clark DJ, Lipworth BJ. Adrenal suppression with chronic dosing of fluticasone propionate compared with budesonide in adult asthmatic patients. *Thorax* 1997;52:55-58.

22. Edsbäcker S, Wollmer P, Selroos O, Borgström L, Olsson B, Ingelf J. Do airway clearance mechanisms influence the local and systemic effects of inhaled corticosteroids? *Pulm Pharmacol Ther* 2007;21:247-258.

23. Lee DK, Haggart K, Currie GP, Bates CE, Lipworth BJ. Effects of hydrofluoroalkane formulations of ciclesonide 400 microg once daily vs fluticasone 250 microg twice daily on methacholine hyper-responsiveness in mild-to-moderate persistent asthma. *Br J Clin Pharmacol* 2004;58:26-33.

24. Thorsson L, Dahlstrom K, Edsbäcker S, Källén A, Paulson J, Wiren JE. Pharmacokinetics and systemic effects of inhaled fluticasone propionate in healthy subjects. *Br J Clin Pharmacol* 1997;43:155-161.

25. Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy 1977;7:235-243.

26. Gallo PP. Center-weighting issues in multicenter clinical trials. *J Biopharm Stat* 2000;10:145-163.

27. Whelan GJ, Blumer JL, Martin RJ, Szefler SJ. Fluticasone propionate plasma concentration and systemic effect: effect of delivery device and duration of administration. *J Allergy Clin Immunol* 2005;116:525-530.

28. Brutsche MH, Brutsche IC, Munawar M, Langley SJ, Masterson CM, Daley-Yates PT, Brown R, Custovic A, Woodcock A. Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study. *Lancet* 2000;356:556-561.

29. Harrison TW, Tattersfield AE. Plasma concentrations of fluticasone propionate and budesonide following inhalation from dry powder inhalers by healthy and asthmatic subjects. *Thorax* 2003;58:258-260.

30. Weiner P, Berar-Yanay N, Davidovich A, Magadle R. Nocturnal cortisol secretion in asthmatic patients after inhalation of fluticasone propionate. *Chest* 1999;116:931-934.

31. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur Respir J* 2006;28:1042-1050.

32. Derendorf H. Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. *J Clin Pharmacol* 2007;47:782-789.

33. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170:836-844.

34. Prosperini G, Rajakulasingam K, Cacciola RR, Spicuzza L, Rorke S, Holgate S. Changes in sputum counts and airway hyperresponsiveness after budesonide: monitoring anti-inflammatory response on the basis of surrogate markers of airway inflammation. *J Allergy Clin Immunol* 2002;110:855-861.

35. Medici TC, Grebski E, Hacki M, Ruegsegger P, Maden C, Efthimiou J. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. *Thorax* 2000;55:375-382.

36. Li JT, Ford LB, Chervinsky P, Weisberg SC, Kellerman DJ, Faulkner KG, Herje NE, Hamedani A, Harding SM, Shah T. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. *J Allergy Clin Immunol* 1999;103:1062-1068.

37. Kraan J, Koëter GH, van der Mark TW, Boorsma M, Kukler J, Sluiter HJ, de Vries K. Dosage and time effects of inhaled budesonide on bronchial hyperreactivity. *Am Rev Respir Dis* 1988;137:44-48.

38. Taylor DA, Jensen MW, Kanabar V, Engelstätter R, Steinijans VW, Barnes PJ, O'Connor BJ. A dose-dependent effect of the novel inhaled corticosteroid ciclesonide on airway responsiveness to adenosine-5'-monophosphate in asthmatic patients. *Am J Respir Crit Care Med* 1999;160:237-243.

39. Nielsen LP, Dahl R. Therapeutic ratio of inhaled corticosteroids in adult asthma. A dose-range comparison between fluticasone propionate and budesonide, measuring their effect on bronchial hyperresponsiveness and adrenal cortex function. *Am J Respir Crit Care Med* 2000;162:2053-2057.

40. Ward C, Pais M, Bish R, Reid D, Feltis B, Johns D, Walters EH. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax* 2002;57:309-316.

41. Peachell PT, Columbo M, Kagey-Sobotka A, Lichtenstein LM, Marone G. Adenosine potentiates mediator release from human lung mast cells. *Am Rev Respir Dis* 1988;138:1143-1151.

42. Polosa R, Li Gotti F, Mangano G, Mastruzzo C, Pistorio MP, Crimi N. Monitoring of seasonal variability in bronchial hyper-responsiveness and sputum cell counts in non-asthmatic subjects with rhinitis and effect of specific immunotherapy. *Clin Exp Allergy* 2003;33:873-881.

43. van den Berge M, Kerstjens HA, Meijer RJ, de Reus DM, Koëter GH, Kauffman HF, Postma DS. Corticosteroid-induced improvement in the PC20 of adenosine monophosphate is more closely associated with reduction in airway inflammation than improvement in the PC20 of methacholine. *Am J Respir Crit Care Med* 2001;164:1127-1132.

44. Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlen B, DiMaria G, Foresi A, Hargreave FE, Holgate ST, Inman M, Lötvall J, Magnussen H, Polosa R, Postma DS, Riedler J. Indirect airway challenges. *Eur Respir J* 2003;21:1050-1068.

45. Phillips K, Oborne J, Lewis S, Harrison TW, Tattersfield AE. Time course of action of two inhaled corticosteroids, fluticasone propionate and budesonide. *Thorax* 2004;59:26-30.

46. Kannies F, Richter K, Böhme S, Jörres RA, Magnussen H. Effect of inhaled ciclesonide on airway responsiveness to inhaled AMP, the composition of induced sputum and exhaled nitric oxide in patients with mild asthma. *Pulm Pharmacol Ther* 2001;14:141-147.

47. Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyperresponsiveness: a meta-analysis. *Ann Allergy Asthma Immunol* 2003;90:194-198.

FIGURES LEGENDS

Fig. 1. Study design

Visits T_0–T_1, T_3–T_4, T_6–T_7, T_9–T_{10} and T_{12}–T_{13} were separated by 7 (±0) days. Visits T_0–T_2, T_3–T_5, T_6–T_8, T_9–T_{11} and T_{12}–T_{14} were separated by 9 (–2/+3) days.

CIC=ciclesonide; FP=fluticasone propionate; T=treatment visit

Fig. 2. Consort diagram showing the flow of the patients. Seq = Sequence.

83 patients were screened. 32 patients received study medication according to one of ten sequences. Two patients discontinued the study for non medical reasons. The sequence of the patient who did erroneously continue to use his Diskus FP on top of his study medication, was a posteriori called sequence 11, since that treatment did not correspond with one of ten sequences originally scheduled before the start of the study.

Fig. 3. Mean serum cortisol mesor (nmol/L) following placebo (PLA), ciclesonide 320 µg/day (CIC 320), ciclesonide 640 µg/day (CIC 640), fluticasone propionate 500 µg/day (FP 500) or fluticasone propionate 1000 µg/day (FP 1000). All treatment groups were administered CIC 160 µg once daily in the evening plus salmeterol 50 µg twice daily. Data are presented as at least squares (LS) mean ± standard error of the LS mean. *$p<0.01$ versus placebo; †$p\leq 0.0057$ versus CIC 320 µg/day; ‡$p=0.0197$ versus CIC 640 µg/day.

Fig. 4. PC_{20} methacholine at intake and after placebo, ciclesonide and fluticasone. All treatment groups were administered CIC 160 µg once daily in the evening plus salmeterol 50 µg twice daily. Same abbreviations as in Fig. 3.

Fig. 5. PC_{20} adenosine at intake and after placebo, ciclesonide and fluticasone. All treatment groups were administered CIC 160 µg once daily in the evening plus salmeterol 50 µg twice daily. Same abbreviations as in Fig. 3.

Table 1. List of the 10 permutations of order, used for the 5 treatments.

Sequence	TI	TII	TIII	TIV	TV
1	CIC 320	CIC 640	PLAC	FP 500	FP 1000
2	CIC 320	PLAC	CIC 640	FP 1000	FP 500
3	CIC 640	CIC 320	FP 500	PLAC	FP 1000
4	CIC 640	FP 500	CIC 320	FP 1000	PLAC
5	FP 500	CIC 640	FP 1000	CIC 320	PLAC
6	FP 500	FP 1000	CIC 640	PLAC	CIC 320
7	FP 1000	FP 500	PLAC	CIC 640	CIC 320
8	FP 1000	PLAC	FP 500	CIC 320	CIC 640
9	PLAC	CIC 320	FP 1000	CIC 640	FP 500
10	PLAC	FP 1000	CIC 320	FP 500	CIC 640

Table 2. Baseline demographics and characteristics.

	N=32
Median age, years	27
Range	18–59
Mean (± SD) weight, kg	70 ± 16
Mean (± SD) height, cm	171 ± 9
Gender, n	
Male	12
Female	20
Race, n	
Caucasian	31
Black	1
ICS pre-treatment, n (%)	
ICS	12
ICS/LABA	20
Smoking Status, n (%)	
Non-smokers	19
Ex-smokers	11
Current smokers	2
Mean (± SD) FEV_1 % predicted*	84.9 ± 13.2
Mean PC_{20} AMP (mg/ml)	16.7 (2.0–60)
Mean PC_{20} MCh (mg/ml)	2.0 (0.1–8.0)

*Taken at randomization

SD=standard deviation; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; FEV_1=forced expiratory volume in 1 second; PC_{20}=provocative concentration leading to a 20% decrease in FEV_1; AMP=adenosine 5-monophosphate; MCh=methacholine.

Table 3. Effects of treatments on serum cortisol mesor and urine cortisol, adjusted for creatinine. Placebo = maintenance dose of CIC 160 µg/day).

	Placebo	**CIC 320 µg/day**	**CIC 640 µg/day**	**FP 500 µg/day**	**FP 1000 µg/day**
Serum cortisol mesor, nmol/L					
	N=27	N=27	N=27	N=27	N=29
Mean ± SD	381.2 ± 98.5	352.8 ± 110.4	341.6 ± 95.9	332.9 ± 94.2	304.4 ± 150.6
LSmean ± SEM	369.2 ± 22.6	341.0 ± 22.7	331.8 ± 22.7	323.0 ± 22.6	293.0 ± 22.3
Difference vs. placebo					
LSmean ± SEM	-	–28.2 ± 18.8	–37.3 ± 18.8	–46.2 ± 19.0	–76.1 ± 18.6
95% CI	-	–65.5, 9.2	–74.7, 0.0	–83.8, –8.5	–112.9, –39.3
p-value	-	0.0251	0.0687	0.0084	<0.0001
Difference vs. FP 1000 µg/day					
LSmean ± SEM	76.1 ± 18.6	48.0 ± 18.6	38.8 ± 18.6	30.0 ± 18.7	-
95% CI	39.3, 112.9	11.1, 84.8	1.9, 75.7	–7.2, 67.1	-
p-value	0.0001	0.0057	0.0197	0.0563	-
Change in serum cortisol to placebo, %					
	-	N=26	N=26	N=25	N=27
Mean ± SD	-	–6.1 ± 26.1	–7.9 ± 18.5	–10.3 ± 20.9	–19.8 ± 28.0
24-hour urine cortisol adjusted for creatine, nmol/mmol					
	N=25	N=26	N=27	N=27	N=28
Mean ± SD	25.74 ± 17.24	22.95 ± 10.17	23.72 ± 10.75	20.49 ± 7.49	20.74 ± 10.93
LSmean ± SEM after treatment	25.04 ± 2.44	22.12 ± 2.43	23.32 ± 2.39	20.06 ± 2.39	19.80 ± 2.37
Difference vs. placebo, LSmean ± SEM	-	–2.92 ± 2.38	–1.72 ± 2.35	–4.98 ± 2.36	–5.24 ± 2.32
95% CI	-	–7.64, 1.80	–6.38, 2.94	–9.66, –0.30	–9.84, –0.64
p-value	-	0.1111	0.2326	0.0186	0.0130

For all safety parameters: the data provided are for the restricted safety analysis, excluding one patient.
CIC=ciclesonide; FP=fluticasone propionate; LS=least squares; SEM=standard error of the LSmean; CI=confidence interval; SD=standard deviation.

Table 4. Least squares mean changes in bone formation markers compared with placebo (= maintenance dose of CIC 160 µg/day).

	CIC 320 µg/day (N=27)	**CIC 640 µg/day (N=27)**	**FP 500 µg/day (N=27)**	**FP 1000 µg/day (N=27)**
P_1NP (µg/L)				
LS mean ± SEM	–2.7 ± 4.1	0.8 ± 4.1	–3.3 ± 4.2	–10.4 ± 4.1
95% CI	–10.9, 5.5	–7.4, 9.0	–11.6, 4.9	–18.4, –2.3
p-value	0.5156	0.8376	0.4258	0.0126
Serum osteocalcin				
(ng/mL)	0.7 ± 1.2	0.0 ± 1.2	–1.8 ± 1.2	–3.3 ± 1.2
LS mean ± SEM	–1.7, 3.0	–2.4, 2.3	–4.2, 0.6	–5.6, –1.0
95% CI	0.5814	0.9799	0.1312	0.0054
p-value				
Bone specific AP (µg/L)				
LS mean ± SEM	0.4 ± 0.4	–0.1 ± 0.4	0.3 ± 0.4	0.0 ± 0.4
95% CI	–0.4, 1.2	–0.9, 0.7	–0.5, 1.1	–0.7, 0.8
p-value	0.3304	0.8710	0.4473	0.9067

CIC=ciclesonide; FP=fluticasone propionate; P_1NP=N-terminal propetide of type 1 procollagen; AP=alkaline phosphatase. P-values are set versus placebo.

Table 5. Change in PC_{20} methacholine and PC_{20} adenosine (doubling doses) compared with placebo (= maintenance dose of CIC 160 µg/day).

Change in PC_{20} (doubling concentrations) versus placebo	**CIC 320 µg/day (N=29)**	**CIC 640 µg/day (N=29)**	**FP 500 µg/day (N=30)**	**FP 1000 µg/day (N=30)**
Methacholine				
LS mean ± SEM	0.3 ± 0.3	0.5 ± 0.3	0.6 ± 0.3	0.7 ± 0.3
95% CI	-0.3, 0.8	0.0, 1.1	0.1, 1.2	0.1, 1.3
p-value	0.3356	0.0645	0.0228	0.0145
Adenosine				
LS mean ± SEM	0.9 ± 0.4	1.6 ± 0.4	1.8 ± 0.4	1.4 ± 0.4
95% CI	0.1, 1.7	0.6, 2.4	1.0, 2.6	0.6, 2.2
p-value	0.0218	≤0.0001	≤0.0001	0.0007

PC_{20}=provocative concentration leading to a 20% decrease in FEV_1; LS=least squares; SEM=standard error; CIC=ciclesonide; FP=fluticasone propionate.

Fig. 1

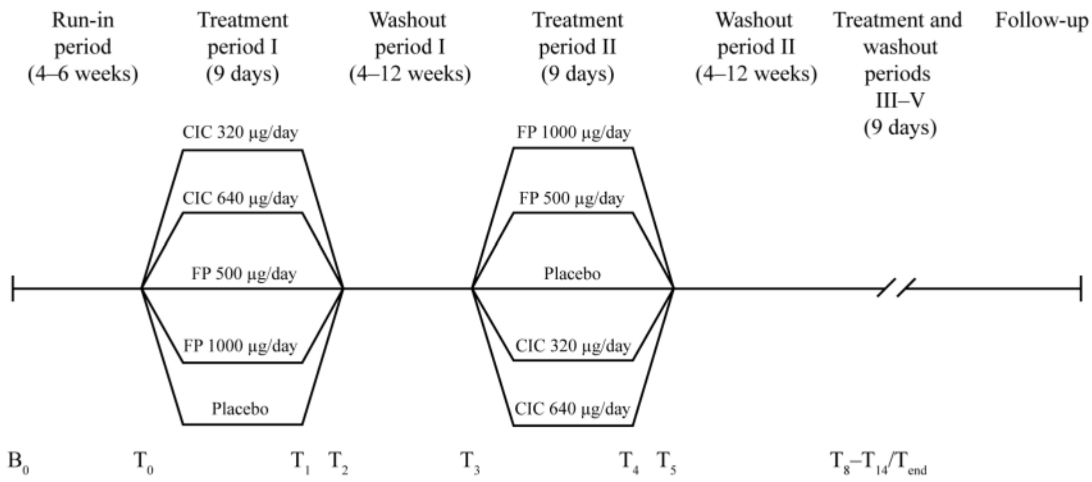

Run-in period (4–6 weeks)
Treatment period I (9 days)
Washout period I (4–12 weeks)
Treatment period II (9 days)
Washout period II (4–12 weeks)
Treatment and washout periods III–V (9 days)
Follow-up
CIC 320 µg/day
CIC 640 µg/day
FP 500 µg/day
FP 1000 µg/day
Placebo
FP 1000 µg/day
FP 500 µg/day
Placebo
CIC 320 µg/day
CIC 640 µg/day
B_0
T_0
T_1
T_2
T_3
T_4
T_5
T_8–T_{14}/T_{end}

Fig. 2

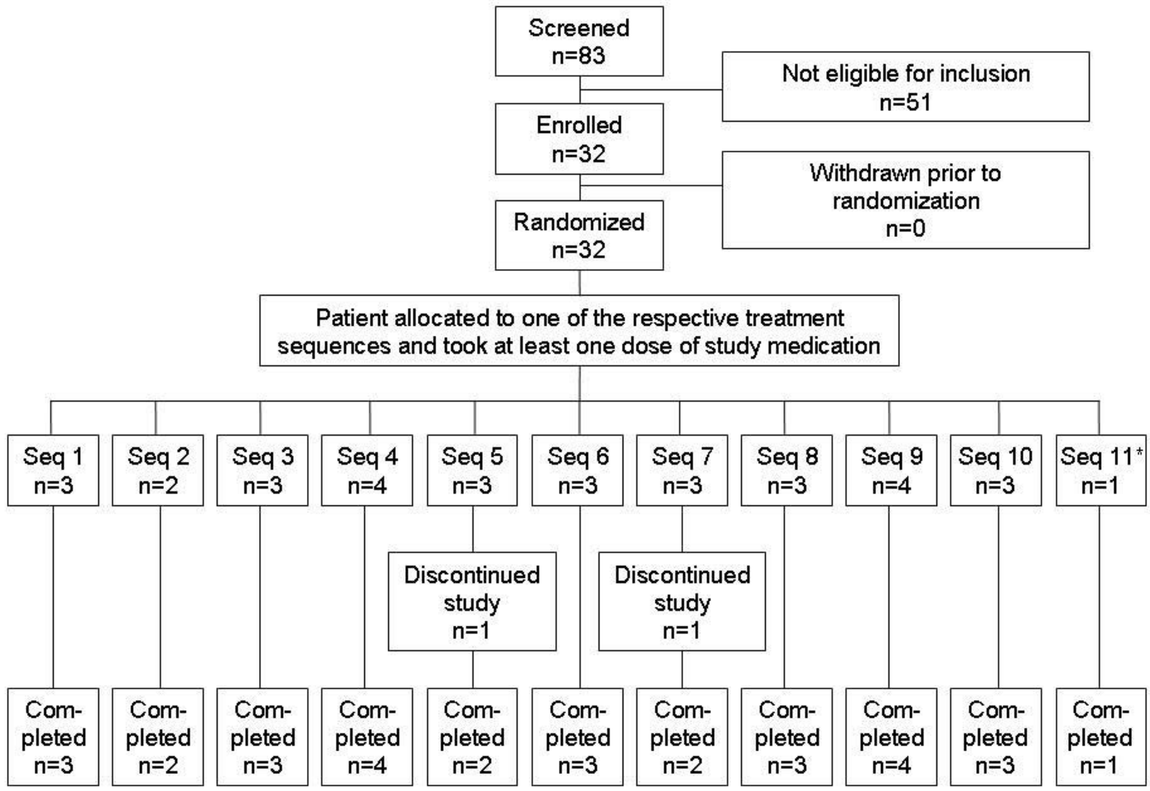

Screened
n=83
Not eligible for inclusion
n=51
Enrolled
n=32
Withdrawn prior to randomization
n=0
Randomized
n=32
Patient allocated to one of the respective treatment sequences and took at least one dose of study medication
Seq 1 n=3
Seq 2 n=2
Seq 3 n=3
Seq 4 n=4
Seq 5 n=3
Seq 6 n=3
Seq 7 n=3
Seq 8 n=3
Seq 9 n=4
Seq 10 n=3
Seq 11* n=1
Discontinued study n=1
Discontinued study n=1
Com-pleted n=3
Com-pleted n=2
Com-pleted n=3
Com-pleted n=4
Com-pleted n=2
Com-pleted n=3
Com-pleted n=2
Com-pleted n=3
Com-pleted n=4
Com-pleted n=3
Com-pleted n=1

Fig. 3

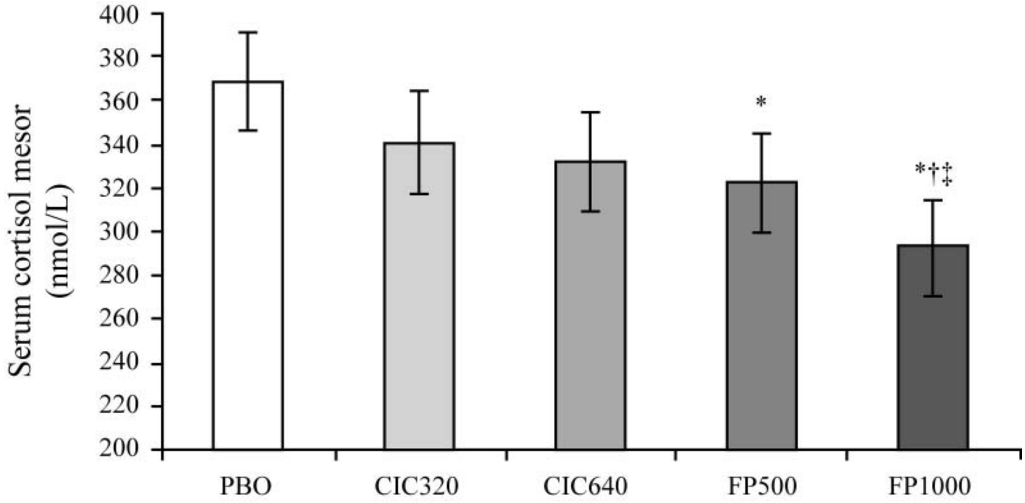
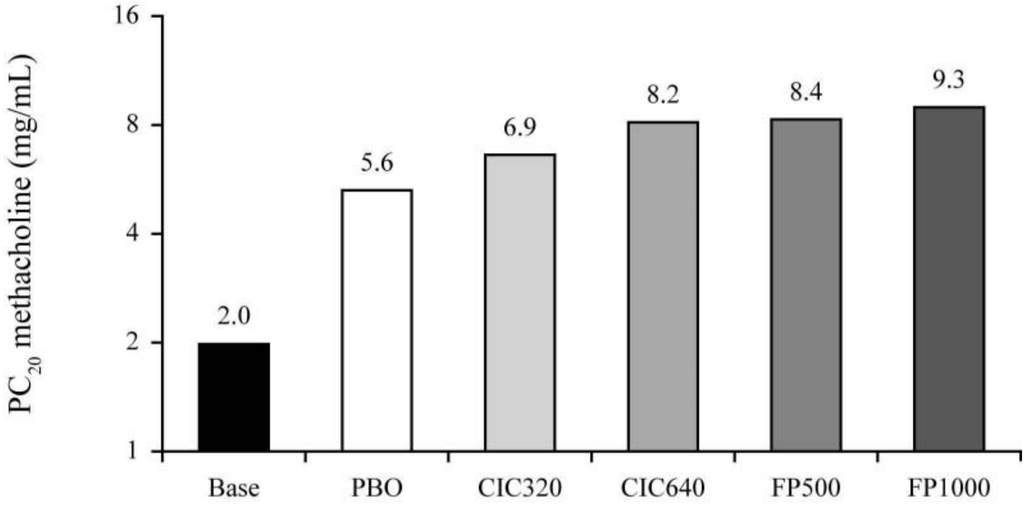
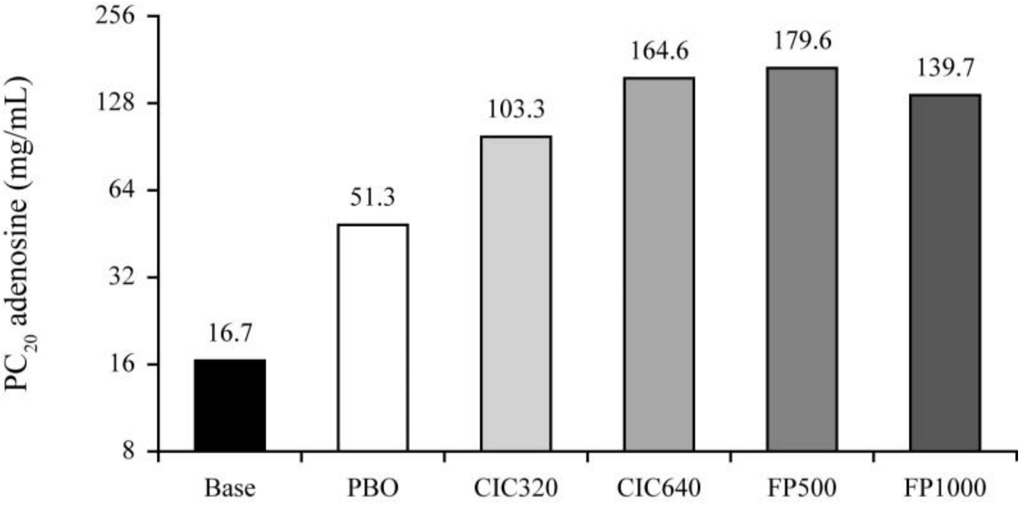

Serum cortisol mesor (nmol/L)
400
380
360
340
320
300
280
260
240
220
200
*
*†‡
PBO
CIC320
CIC640
FP500
FP1000

Fig. 4



16
8
4
2
1
PC20 methacholine (mg/mL)
2.0
5.6
6.9
8.2
8.4
9.3
Base
PBO
CIC320
CIC640
FP500
FP1000

Fig. 5


256
128
64
32
16
8
PC20 adenosine (mg/mL)
16.7
51.3
103.3
164.6
179.6
139.7
Base
PBO
CIC320
CIC640
FP500
FP1000