Airway and Systemic Effects of Hydrofluoroalkane Formulations of High-Dose Ciclesonide and Fluticasone in Moderate Persistent Asthma*

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Background: **There are no data comparing the relative effects of high-dose ciclesonide (CIC) and fluticasone propionate (FP) on airway and systemic outcomes in patients with moderate persistent asthma.**

Objective: **We elected to evaluate the relative effects of CIC and FP on the plasma cortisol response to stimulation with human corticotropin-releasing factor (hCRF) and bronchial hyperresponsiveness to methacholine as the primary outcome variables, in addition to secondary outcomes of overnight 10-h urinary cortisol (OUC) levels, exhaled nitric oxide levels, lung function, symptoms, and quality of life.**

Methods: **Fourteen patients with moderate persistent asthma (mean FEV_1, 67% predicted [prior to each randomized treatment]) completed the study, which had a randomized, double-blind, double-dummy, crossover design, per protocol. Patients stopped receiving their usual inhaled corticosteroids for the duration of the study and instead began receiving salmeterol, 50 μg twice daily, and montelukast, 10 mg once daily, for the 2-week washout periods prior to each randomized treatment, in order to prevent dropouts after withdrawal from inhaled corticosteroid therapy. Patients received 4 weeks of either CIC, 200 μg ex-valve (160 μg ex-actuator) four puffs twice daily, plus FP-placebo, four puffs twice daily, or FP, 250 μg ex-valve (220 μg ex-actuator) four puffs twice daily, plus CIC-placebo, four puffs twice daily. Salmeterol and montelukast were withheld for 72 h prior to each postwashout baseline visit, and CIC or FP was withheld for 12 h prior to each posttreatment visit.**

Results: **FP, but not CIC, when compared to respective baseline values, significantly suppressed ($p < 0.05$) plasma cortisol levels as follows: FP prior to receiving hCRF: geometric mean fold difference, 1.2; 95% confidence interval (CI), 1.1 to 1.3; CIC prior to receiving hCRF: geometric mean fold difference, 0.9; 95% CI, 0.8 to 1.0; FP 30 min after receiving hCRF: geometric mean fold difference, 1.2; 95% CI, 1.1 to 1.3; CIC 30 min after receiving hCRF: geometric mean fold difference, 1.0; 95% CI, 0.9 to 1.2; OUC after FP administration: geometric mean fold difference, 1.9; 95% CI, 1.4 to 2.6; OUC after CIC administration: geometric mean fold difference, 1.2; 95% CI, 0.9 to 1.5. There was also a significantly lower ($p < 0.05$) mean value for OUC levels after FP administration than after CIC administration (geometric mean fold difference, 1.5; 95% CI, 1.1 to 2.0). Therapy with CIC and FP, compared to respective baselines, significantly increased ($p < 0.05$) the provocative concentration of methacholine causing a 20% fall in FEV_1, as follows: CIC: doubling dilution difference, 0.8; 95% CI, 0.1 to 1.6; FP: doubling dilution difference, 1.0; 95% CI, 0.1 to 2.0. It also significantly reduced ($p < 0.05$) exhaled nitric oxide levels, as follows: CIC: geometric mean fold difference, 1.2; 95% CI, 1.1 to 1.3; FP: geometric mean fold difference, 1.9; 95% CI, 1.3 to 2.8. There was no effect on other secondary efficacy outcomes.**

Conclusion: **FP, 2,000 μg daily, but not CIC, 1,600 μg daily, significantly suppressed hypothalamic-pituitary-adrenal axis outcomes, with OUC levels being lower after FP administration than after CIC administration. Both drugs significantly improved airway outcomes in terms of methacholine bronchial hyperresponsiveness and exhaled nitric oxide levels. The present results would therefore suggest that CIC might confer a better therapeutic ratio than FP when used at higher doses.**

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Key words: asthma; ciclesonide; exhaled nitric oxide; fluticasone propionate; human corticotropin-releasing factor; methacholine bronchial challenge; Mini-Asthma Quality-of-Life Questionnaire; overnight 10-h urinary cortisol

Abbreviations: CI = confidence interval; CIC = ciclesonide; $FEF_{25–75}$ = forced expiratory flow, midexpiratory phase; FP = fluticasone propionate; hCRF = human corticotropin-releasing factor; HPA = hypothalamic-pituitary-adrenal; Mini-AQLQ = Mini-Asthma Quality-of-Life Questionnaire; OUC = overnight 10-h urinary cortisol; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV_1

Ciclesonide (CIC) is a topically active, potent inhaled corticosteroid that is currently undergoing the late stages of clinical development. It is a prodrug, which is converted on site by esterase activity in the lung to its active metabolite, desisobutyryl-CIC. The extrafine hydrofluoroalkane solution formulation of CIC produces 50% respirable dose delivery and high pulmonary bioavailability for the active moiety. However, the active moiety has 99% plasma protein binding, resulting in a very low concentration of free unbound desisobutyryl-CIC being present in the systemic circulation, which, along with almost complete hepatic first-pass metabolism for the swallowed fraction and rapid clearance, produce a favorable systemic safety profile. This has been borne out by preliminary data showing no significant hypothalamic-pituitary-adrenal (HPA) axis suppression with CIC at a daily dose of up to 1,600 μg, on a variety of end points, including 24-h integrated plasma and urine cortisol profiles, as well as the dynamic adrenocorticotropic hormone-stimulated cortisol response.[1–4] Another sensitive method of dynamic stimulation testing is the 100-μg bolus human corticotropin-releasing factor (hCRF) stimulation test.[5] This has been shown to be as sensitive as the insulin stress test for detecting impaired adrenal reserves in corticosteroid-treated patients.[6]

In order to evaluate the therapeutic ratio, it is also important to consider the effects on sensitive airway efficacy outcomes, such as bronchial hyperresponsiveness. In this respect, bronchial hyperresponsiveness to methacholine is more closely related to asthmatic inflammation than to lung function, when assessing the response to inhaled corticosteroids.[7,8] We have previously shown that hydrofluoroalkane formulations of CIC, 400 μg daily, and fluticasone propionate (FP), 500 μg daily for 4 weeks, exhibit equivalent efficacy on bronchial hyperresponsiveness to methacholine challenge in patients with mild-to-moderate asthma.[9]

The purpose of the present study was to evaluate the relative airway and systemic effects of hydrofluoroalkane formulations of CIC, 200 μg four puffs twice daily, and FP, 250 μg four puffs twice daily, on hCRF cortisol response and on methacholine bronchial hyperresponsiveness (the primary systemic and airway outcomes, respectively) in patients with moderate, persistent asthma, in order to ascertain the relative therapeutic ratio of these two drugs.

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Materials and Methods

Patients

Eligible patients were nonsmokers with moderate, persistent asthma[10,11] who had been stable for at least 3 months prior to the study and had not received a course of oral corticosteroids or antibiotics during this period. Patients were required to be receiving either inhaled corticosteroids alone in a daily dose of up to 2,000 μg beclomethasone dipropionate/2,000 μg budesonide/1,000 μg FP or half the dose of the above inhaled corticosteroids in combination with second-line controller therapy such as with long-acting β_2-agonists or leukotriene receptor antagonists. Patients were required to exhibit airway hyperresponsiveness to methacholine on bronchial challenge testing with a provocative dose of methacholine causing a 20% fall in FEV_1 (PC_{20}) of < 4.0 mg/mL.[12] Informed consent was obtained from all patients, and the Tayside Committee on Medical Research Ethics approved the study.

Study Design

The study design schematic is shown in Figure 1. The study was conducted in a randomized, double-blind, double-dummy, crossover fashion. Patients were required to stop receiving their usual inhaled corticosteroids along with their second-line controller therapy for the duration of the study. Patients began receiving salmeterol (Serevent Accuhaler; GlaxoSmithKline; Uxbridge, UK), 50 μg one puff twice daily, and montelukast (Singulair; Merck Sharp & Dohme Ltd; Hoddesdon, UK), 10 mg once daily during the 2-week washout periods prior to each randomized treatment, in order to prevent dropouts after inhaled corticosteroid withdrawal. Patients were randomized to receive for 4 weeks either hydrofluoroalkane formulations of CIC (Alvesco; Altana Pharma AG; Konstanz, Germany), 200 μg ex-valve (160 μg ex-actuator) four puffs twice daily (8:00 AM and 8:00 PM), plus FP-placebo, four puffs twice daily (8:00 AM and 8:00 PM), or FP (Flixotide Evohaler; GlaxoSmithKline), 250 μg ex-valve (220 μg ex-actuator) four puffs twice daily (8:00 AM and 8:00 PM), plus CIC-placebo, four puffs twice daily (8:00 AM and 8:00 PM). Active and placebo devices for each drug were masked to make them identical in external physical appearance. Salmeterol and montelukast were withheld for 72 h prior to each baseline visit after each washout period, and CIC or FP was withheld for 12 h prior to each study visit. A compliance of at least 90% with study medication was required on a tick chart for data inclusion.

Measurements

Plasma and Urinary Cortisol: Patients attended the laboratory at 7.30 AM and rested in a supine position for 30 min. Following this, patients had blood samples taken for determination of basal plasma cortisol levels at 8:00 AM, and voided their bladders for the last time. The total collected urine thus represented an overnight 10-h excretion (10:00 PM to 8:00 AM) with patients having last emptied their bladder at 10:00 PM the previous night, and having had the last dose of CIC or FP at 8:00 PM. After