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High lung deposition of ^{99m}Tc-labeled ciclesonide administered via HFA-MDI to patients with asthma

Steve Newman[a], Andrew Salmon[a], Ruediger Nave[b], Anton Drollmann[b,*]

[a]*Pharmaceutical Profiles, Nottingham, UK*
[b]*Altana Pharma AG, Byk-Gulden-Str. 2, 78467 Konstanz, Germany*

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Summary
Objective: To examine the deposition and pharmacokinetics of ciclesonide administered via hydrofluoroalkane-metered dose inhaler (HFA-MDI) in patients with asthma.
Methods: Twelve patients with mild asthma (FEV_1, 95% predicted) inhaled a single dose of ^{99m}technetium (Tc)-ciclesonide 320 μg ex-actuator (400 μg ex-valve). Deposition of ciclesonide in the lung and oropharynx was quantified using two-dimensional (2D)-gamma scintigraphy. Three-dimensional single photon emission computed tomography (3D SPECT) was used to assess the regional distribution of ciclesonide in the lung. The pharmacokinetics of ciclesonide and its active metabolite, desisobutyryl-ciclesonide (des-CIC), were determined by liquid chromatography-tandem mass spectrometry. Ciclesonide and des-CIC concentrations were determined in mouth-rinsing solutions.
Results: 2D-gamma scintigraphy indicated that ciclesonide deposition was higher in the whole lung (52%) than in the oropharynx (32.9%). Furthermore, 3D SPECT revealed that ciclesonide deposition within the lungs was highest in the peripheral regions that contain the small airways and alveoli. The pharmacokinetic profile of Tc-labeled ciclesonide and des-CIC was similar to that obtained after inhalation of non-labeled formulations in previous studies. Des-CIC accounted for 14.9% of the total molar concentration of ciclesonide/des-CIC in mouth-rinsing solutions obtained between 7 and 12 min after inhalation.
Conclusion: Inhalation of ciclesonide via HFA-MDI results in high pulmonary deposition, especially in the peripheral regions of the lung. High pulmonary deposition contributes to ciclesonide's ability to maintain lung function and control symptoms in patients with asthma. Deposition and activation of ciclesonide in the oropharynx is low, consistent with previous reports of low oropharyngeal deposition and a reduced incidence of local side effects in patients receiving ciclesonide therapy.

*Corresponding author. Tel.: +49 7531 84 2361; fax: +49 7531 84 92361.
E-mail address: anton.drollmann@altanapharma.com (A. Drollmann).

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Introduction

Asthma, one of the most common chronic diseases, results from complex interactions among inflammatory cells, mediators, and the tissues and cells in the airways and is characterized by airway obstruction, airway inflammation, and airway hyperresponsiveness.[1] Inhaled corticosteroids (ICS) are the most effective agents available to treat inflammation associated with mild asthma.[1] The reduction in chronic airway inflammation produced by ICS results in improved pulmonary function.[2] However, treatment with ICS may cause local and systemic side effects, such as reduction of bone formation, reduction of growth velocity in children, skin bruising, and down-regulation of endogenous cortisol release.[3,4] Therefore, ideally, systemic exposure to ICS should be minimized.

Ciclesonide is a nonhalogenated ICS for the treatment of asthma. Ciclesonide inhibits the inflammatory response, including the activation of lymphocytes and the infiltration of inflammatory cells into the airways.[5] Clinical studies show that ciclesonide significantly improves pulmonary function and reduces airway hyperresponsiveness in patients with asthma.[6,7] Ciclesonide is delivered as an inactive parent compound to the lungs, where it is converted by esterases to the active metabolite, desisobutyryl-ciclesonide (des-CIC). Subsequently, des-CIC is metabolized to inactive metabolites in the liver by cytochrome P-450 enzymes.[8]

Because ciclesonide and des-CIC have almost no oral bioavailability,[9] the pharmacokinetics (PK) of ciclesonide in serum depends largely on pulmonary deposition. Ciclesonide is administered as an aerosol using a hydrofluoroalkane-134a metered-dose inhaler (HFA-MDI). In a previous study, more than 50% of the administered dose of ciclesonide was deposited in the lungs of healthy volunteers.[10] However, deposition of ciclesonide in the lung may be impaired by the inflammation of the small airways in patients with asthma. Bronchial obstruction is also a determinant of aerosol distribution within the lungs of asthma patients, and increased bronchial obstruction enhances central airway deposition of inhaled particles.[11] For example, inhaled budesonide is more centrally deposited in the lung in patients with asthma than in healthy volunteers.[12,13] The current study investigated pulmonary deposition of ciclesonide in patients with mild asthma. Furthermore, this study assessed serum PK and oropharyngeal deposition of ciclesonide and des-CIC.

Methods

Patients

Male and female patients with clinical symptoms of asthma, a forced expiratory volume in 1 s (FEV_1) $\geqslant$80% predicted, and an FEV_1/forced vital capacity (FVC) ratio of <0.85 were eligible to participate in this study. Eligible patients were between the ages of 18 and 65 years, of normal weight (Broca index: $0.80 \leqslant \text{weight}/[\text{height}-100] \leqslant 1.25$), and were non-smokers. Patients could receive anti-asthma medication administered according to the same schedule throughout the study and/or short-acting beta (β)-agonists as rescue medication until 4 h before ciclesonide inhalation.

Patients with a clinically active disease other than asthma, clinically relevant allergies, hoarseness or oropharyngeal candidiasis, upper respiratory tract infection within 14 days of the first study day, or a lower respiratory tract infection within the last 3 months were not eligible to participate in this study. A negative drug test, negative hepatitis test, and no history of drug or alcohol abuse were also required. Women of childbearing age were required to use an effective method of birth control. The study was conducted at Pharmaceutical Profiles Ltd. (Nottingham, UK) in accordance with the revised Declaration of Helsinki and the requirements of Good Clinical Practice.

Study design

This study had a single-dose, nonrandomized, open-label design. Each patient received a single dose of 320 μg ^{99m}Technetium (Tc)-ciclesonide ex-actuator (2 puffs of 160 μg; equivalent to 2 puffs of 200 μg ex-valve). The primary study variable was the total and regional distribution of ciclesonide in the lungs, oropharynx, and exhaled air. Secondary variables included the PK properties of ciclesonide and des-CIC: area under the concentration curve from 0 to infinity (AUC_{0-inf}), maximum serum concentration (C_{max}), terminal half-life ($t_{1/2}$), time to reach maximum concentration (t_{max}), and the concentration of ciclesonide and des-CIC in mouth-rinsing solutions. Safety and tolerability of ciclesonide were also assessed.

Radiolabeling of the ciclesonide formulation

A method for radiolabeling the ciclesonide formulation using the radionuclide ^{99m}Tc was developed and validated according to methodologies used in previous studies in which deposition from an MDI

was assessed.[13,14] The radiolabeling method was validated by comparing the size distributions of ciclesonide and ^{99m}Tc in an Andersen cascade impactor, operated at a flow rate of 28.3 L/min.

Administration of the radiolabeled ciclesonide formulation

Patients inhaled 2 doses, approximately 1 min apart, of radiolabeled ciclesonide 160 μg (ex-actuator, equivalent to 200 μg ex-valve) from an MDI. Patients were instructed to inhale slowly and deeply, and the MDI was actuated by an investigator during inhalation. After inhaling, patients held their breath for 10 s and then exhaled via a low-resistance filter.

Measurement of lung function

Pulmonary function tests (FEV_1, FVC, and peak expiratory flow [PEF] rate) were performed at screening, before dosing, at 1 and 14 h after dosing on the study day, and at the poststudy visit. All tests were performed using a MicroLoop Spirometer (Micro Medical Ltd., Rochester, Kent, UK).

Scintigraphic assessment of lung deposition

Distribution of ^{99m}Tc-ciclesonide in the lungs, oropharynx, esophagus, stomach, and exhaled air was assessed using two-dimensional (2D) gamma scintigraphy and three-dimensional single photon emission computed tomography (3D SPECT) imaging. Gamma scintigraphy was used to quantify the total amount of drug deposited in the whole lung, oropharynx, esophagus, stomach, and exhaled air filter,[14] whereas 3D SPECT imaging examined the distribution of drug within the lungs in 3 dimensions.[15–17]

Imaging was performed in the following sequence, using a Philips/ADAC Forte twin-headed gamma camera coupled to a data-processing unit (Philips Medical Systems, Surrey, UK): 2D-gamma scintigraphy (anterior and posterior planar images of the lungs and stomach, and lateral images of the oropharynx immediately after dosing), 3D SPECT, and repeat 2D-gamma scintigraphy of the lungs. The planar lung images were corrected for the effects of gamma ray attenuation by overlying tissues. Planar lung images obtained before and after SPECT imaging were compared to correct the SPECT data for clearance of radiotracer from the lungs into the systemic circulation. Patients were supine with their arms above their heads during the imaging procedure, which was completed within 20–25 min of their inhaling the radiolabeled drug formulation. Either at the end of the ^{99m}Tc imaging sequence or on a separate day, each patient inhaled krypton-81m (^{81m}Kr) from a generator, and the resulting ventilation scan was used to obtain a 2D outline of the lungs.

Analysis of the 3D SPECT imaging focused on the right lung to avoid possible artifacts caused by heart and stomach overlap. To determine the amount of ciclesonide deposited in regions containing airways of different sizes, the right lung was divided into 6 concentric lung-shaped shells centered on the hilum (Fig. 1).[18] Shell 1 represented the innermost region of the lung and shell 6 represented the outermost (peripheral) region of the lung. Shell thickness was calculated by dividing the distance between the hilum and the lung edge by 6. The lung edge was defined using data acquired from a SPECT transmission scan using gadolinium-153 (^{153}Gd) line sources that are integral to the Philips/ADAC Forte gamma camera. The count in each of the 6 concentric shells was expressed as a percentage of the total right lung count. These values were then multiplied by the

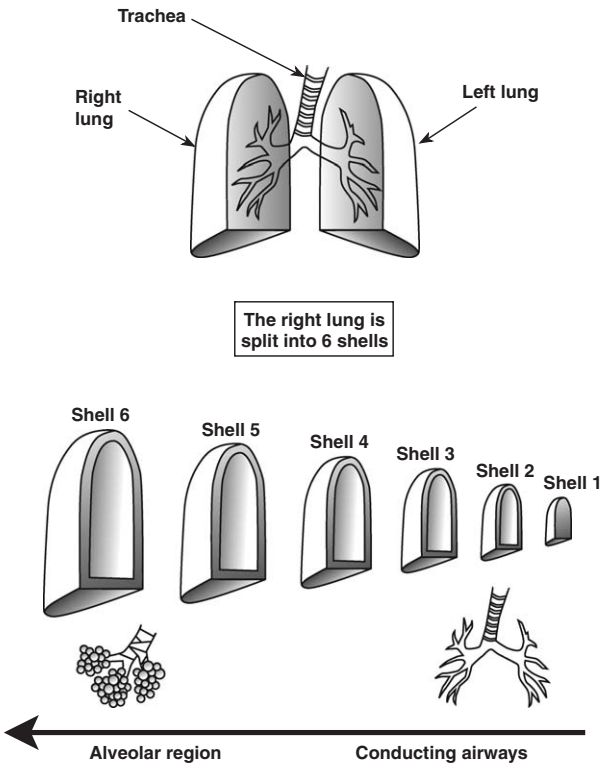

Figure 1 Schematic representation of the shell analysis system used to determine the regional distribution of ciclesonide within the lung. The innermost shells (1 and 2) represent large central airways, whereas the outermost shells (5 and 6) represent the small peripheral airways. Copyright© 2006 from Newman.[18] Reproduced by permission of Routledge/Taylor & Francis Group, LLC.

mass of drug deposited in the right lung (obtained from the planar 2D data) to determine the mass of drug deposited per shell.

Blood sampling

Serial blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 14 h after dosing to determine des-CIC and ciclesonide PK. Approximately 8.5 mL of blood was placed in nonheparinized tubes and allowed to clot for 30 min at 4 °C. Samples were centrifuged at 1550*g* at 4 °C for 10 min. The serum was transferred to clean tubes, stored at −20 °C until the ^{99m}Tc decayed to background levels, and analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Mouth-rinsing samples

Directly after oropharyngeal imaging (approximately 7–12 min postdose), patients rinsed their mouths by gargling twice with 30-mL aliquots of a 50% (v:v) ethanol:water solution. The mouth-rinsing samples were combined and stored at −20 °C until ^{99m}Tc decayed to background levels, and ciclesonide and des-CIC concentrations were determined by LC-MS/MS. Immediately after the mouth-rinsing procedure, patients rinsed their mouths with 100 mL mineral water.

Pharmacokinetic analysis of des-CIC and ciclesonide

Serum and mouth-rinsing samples were analyzed at MDS Pharma Services (Fehraltorf, Switzerland). Ciclesonide and des-CIC were isolated from human serum using solid-phase extraction; serum samples (0.5 mL) were diluted with 2 mL 100 mmol/L phosphate buffer (pH 2.8) and applied to solid-phase extraction cartridges (Isolute C8; Phenomenex, Cheshire, UK). Cartridges were washed twice with 50% methanol in water and the analytes were eluted with 1 mL acetonitrile, which was subsequently evaporated.

Ciclesonide and des-CIC concentrations were determined using reversed-phase HPLC with MS/MS detection. The limits of quantitation using 0.5 mL of human serum were 10 pg/mL for des-CIC and 25 pg/mL for ciclesonide. Assay precision (coefficient of variation) was ⩽8.4% for des-CIC and ⩽2.1% for ciclesonide. Deuterated ciclesonide and des-CIC served as internal standards.

Des-CIC and ciclesonide concentrations were determined in mouth-rinsing samples without sample cleanup. Des-CIC was quantified by reversed-phase HPLC with MS/MS detection. HPLC-MS/MS assay precision was ⩽1.3% for des-CIC, and the limit of quantitation of des-CIC was 1 ng/mL using 0.2 mL of mouth-rinsing sample. Deuterated des-CIC served as internal standard. Ciclesonide was quantified using LC-MS/MS analysis. Assay precision was ⩽2.5% for ciclesonide. Using 0.2 mL of mouth-rinsing solution, the limit of quantitation of ciclesonide was 10 ng/mL.

Safety

Adverse events were recorded throughout the study. Vital signs, 12-lead electrocardiogram, and clinical chemistries were obtained before and after the study.

Statistical analysis

Study variables, including the deposition of ciclesonide and the PK characteristics of ciclesonide and des-CIC, were analyzed in a descriptive manner using summary statistics such as mean and standard deviation (SD). Pharmacokinetic analysis was performed using KINTPC (ALTANA Pharma, version 2.1) software.

Results

Patient demographics

This study was conducted in 12 patients (7 male and 5 female) with mild asthma (Table 1). Mean FEV_1 at

Table 1 Patient demographics and baseline characteristics.

Characteristic	
Median age, years (range)	37 (23–50)
Median height, cm (range)	170 (163–188)
Median weight, kg (range)	77 (58–94)
Broca index (range)	1.05 (0.85–1.24)
Sex, *n* (%)	
Male	7 (58)
Female	5 (42)
Smokers, *n* (%)	0 (0)
Nonsmokers, *n* (%)	12 (100)
FEV_1 at screening	
Measured, mean, L (SD)	3.41 (0.7)
% Predicted, mean (SD)	94.58 (7.5)

FEV_1 = Forced expiratory volume in 1 s; SD = standard deviation.

Table 2 Lung function.

Variable	Predose	1 h postdose	14 h postdose
FEV_1			
Measured, L	3.50 ± 0.80	3.48 ± 0.81	3.43 ± 0.72
% Predicted	97.25 ± 10.26	96.42 ± 8.44	95.58 ± 7.53
FVC, L	4.84 ± 1.11	4.85 ± 1.03	4.80 ± 1.01
PEF, L/s	8.30 ± 1.95	8.07 ± 1.70	8.28 ± 1.71
FEV_1/FVC	0.72 ± 0.06	0.72 ± 0.04	0.72 ± 0.05

Data are presented as means ± standard deviation (SD). $N = 12$.

baseline was approximately 95% predicted. The median age was 37 years, and all patients were nonsmokers and of normal weight. Each patient completed the study without any relevant protocol deviations.

Lung function

Lung function variables (FEV_1, FVC, and PEF by spirometry) remained stable in all patients throughout the treatment period (Table 2).

Radiolabeling validation data

The distributions of drug before labeling, of drug after labeling, and of radiolabel were similar (Fig. 2). These results indicated that the radiolabeling process did not change the particle size distribution, and that the radiolabel was a satisfactory marker for the drug in each particle size band. The mean ± SD fine particle fraction (percentage recovered from stage 2 to final filter of the Andersen cascade impactor) was 60.7 ± 2.8% for drug before labeling, 61.6 ± 8.4% for drug after labeling, and 61.5 ± 8.7% for radiolabel. The validation data allowed the scintigraphic study to proceed. The particle size distributions of each inhaler used on study days were also assessed, and the distributions of ^{99m}Tc within each particle size band were similar to those tested before the study.

Deposition of ciclesonide

2D gamma scintigraphy indicated that a higher percentage of the ex-actuator dose of ciclesonide was deposited in the lungs (52 ± 9.0%) compared with the oropharynx (32.9 ± 13.3%), esophagus (6.2 ± 3.8%), stomach (5.2 ± 5.3%), and exhaled air (3.7 ± 3.1%) (Table 3; Fig. 3). Deposition in the right lung accounted for 27.2 ± 5.6% of the ex-actuator dose (Table 4). Analysis of individual patient data confirmed high deposition of ciclesonide in the

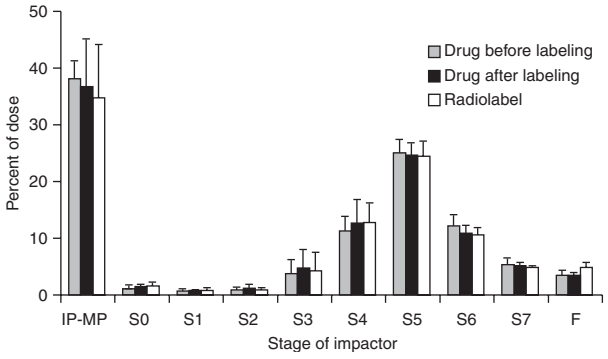

Figure 2 Radiolabeling validation data showing the mean distribution ± SD of drug before labeling ($n = 3$), drug after labeling ($n = 4$), and radiolabel ($n = 4$) with an Andersen cascade impactor. Stages of the impactor are as follows: IP-MP = inlet port-mouthpiece; S0–S7 = stages 0–7; F = final filter.

lungs (Fig. 4). 3D SPECT revealed that the mean deposition of ciclesonide was highest in the 2 outermost shells of the right lung, shell 5 (7.2 ± 1.6% of the ex-actuator dose) and shell 6 (8.0% ± 1.7% of the ex-actuator dose). Examination of individual patient data further confirmed high deposition of ciclesonide in the outermost shells of the lung (Fig. 5). These shells are the ones most likely to contain small airways and alveoli. Expressed on a mass basis, pulmonary deposition of ciclesonide per puff was as follows: whole right lung = 43.6 ± 9.0 μg; inner shells 1–4 = 19.3 ± 7.0 μg; and outer shells 5 and 6 = 24.3 ± 5.3 μg.

Although ciclesonide and des-CIC were both present in patient mouth-rinsing solutions, activation of ciclesonide within the oropharynx was low; the mean concentration ± SD of ciclesonide was 118.7 ± 57.0 μg/L (219.5 ± 105.5 nmol/L) and des-CIC was 18.6 ± 13.0 μg/L (39.5 ± 27.5 nmol/L) (Table 5). Therefore, des-CIC represented only 14.9 ± 4.9% of the mean total molar concentration of ciclesonide related metabolites in mouth-rinsing solutions.

Table 3 Two-dimensional gamma scintigraphy analysis of the percentage distribution of ciclesonide 320 μg*.

Site	Mean percentage deposition ± SD	Median percentage deposition
Whole lung	52.0 ± 9.0	53.2
Oropharynx	32.9 ± 13.3	30.0
Esophagus	6.2 ± 3.8	7.7
Stomach	5.2 ± 5.3	3.6
Exhaled air	3.7 ± 3.1	2.9

SD = standard deviation.
*Ex-actuator, equivalent to 400 μg ex-valve.

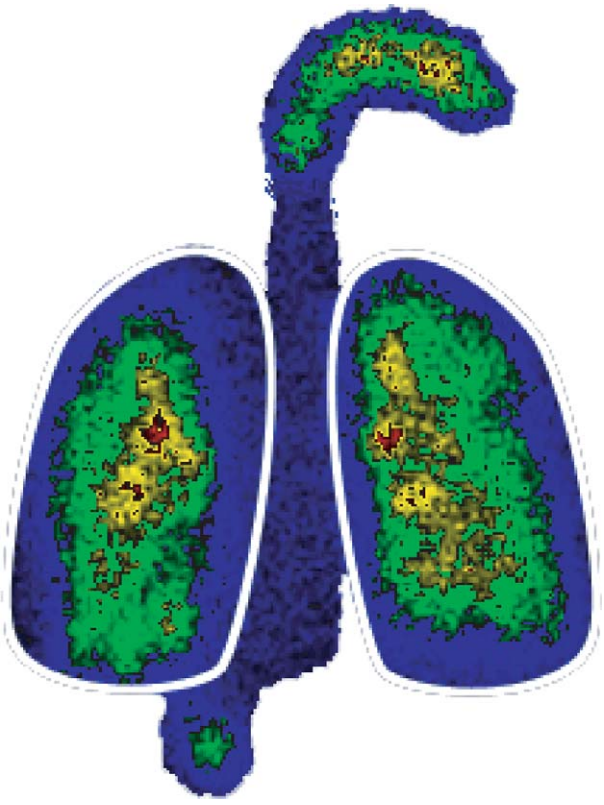

Figure 3 Two-dimensional planar imaging of the pattern of ciclesonide deposition in the human body, with greatest deposition occurring in the lung.

Pharmacokinetics

In addition to the assessment of lung deposition, the $AUC_{(0-inf)}$, C_{max}, T_{max}, and $t_{1/2}$ of ciclesonide and des-CIC were determined. Serum levels of ciclesonide achieved a maximum concentration (C_{max}) of 1.36 ± 0.53 μg/L (mean ± SD) at the first blood sampling time point, 0.25 h after administration (T_{max}) (Table 6). The $AUC_{(0-inf)}$ of ciclesonide was 0.68 ± 0.26 μg. h/L. Distribution and elimination of ciclesonide were rapid with a mean $t_{1/2}$ of 0.57 ± 0.08 h (Table 6; Fig. 6). The mean C_{max} of des-CIC (0.41 ± 0.11 μg/L [mean ± SD]), was achieved approximately 0.94 ± 0.39 h after inhalation (T_{max}). Des-CIC had a mean elimination $t_{1/2}$ of 6.02 ± 1.55 h and an $AUC_{(0-inf)}$ of 1.87 ± 0.66 μg. h/L.

Table 4 3D SPECT analysis of the distribution of ^{99m}Tc-ciclesonide 160 μg* in each of the 6 shells of the right lung.

Shell	Mass of ciclesonide, mean μg per puff ± SD	Ex-actuator dose, mean % ± SD	Deposited dose, %
1	0.3 ± 0.3	0.2 ± 0.2	0.7
2	2.9 ± 1.3	1.8 ± 0.8	6.7
3	7.3 ± 2.8	4.5 ± 1.8	16.7
4	8.8 ± 2.6	5.5 ± 1.6	20.2
5	11.5 ± 2.6	7.2 ± 1.6	26.4
6	12.8 ± 2.7	8.0 ± 1.7	29.4
Sum	43.5 ± 9.0	27.2 ± 5.6	100.0

3D SPECT = 3-dimensional single photon emission computed tomography; ^{99m}Tc = ^{99m}technetium; SD = standard deviation.
Shell 1 represents the innermost (central) region of the lung; Shell 6 represents the outermost (peripheral) region of the lung.
*Ex-actuator (equivalent to 200 μg ex-valve). Patients received a total dose of ciclesonide 320 μg ex-actuator (equivalent to 400 μg ex-valve).

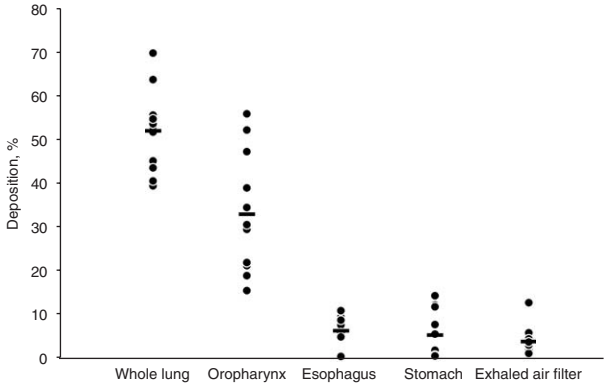

Figure 4 Percent of ciclesonide deposition in the whole lung, oropharynx, esophagus, stomach, and exhaled air filter in 12 patients after inhalation of ciclesonide 320 μg ex-actuator (equivalent to 400 μg ex-valve). Mean data are presented as a solid line.

Safety

Ciclesonide 320 μg ex-actuator was safe and well tolerated in this study. Three treatment-emergent

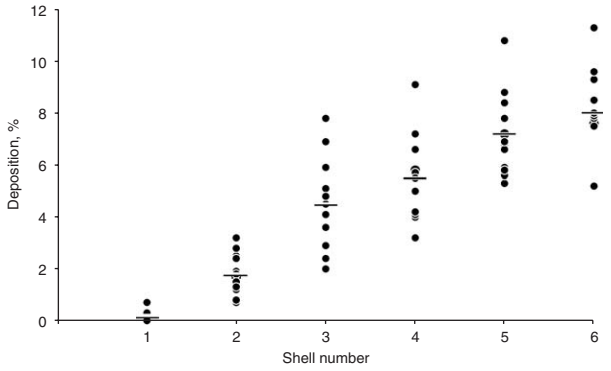

Figure 5 Percent of ciclesonide deposition in shells 1–6 of the lungs of 12 patients after inhalation of ciclesonide 320 μg ex-actuator (equivalent to 400 μg ex-valve). Mean data are presented as a solid line.

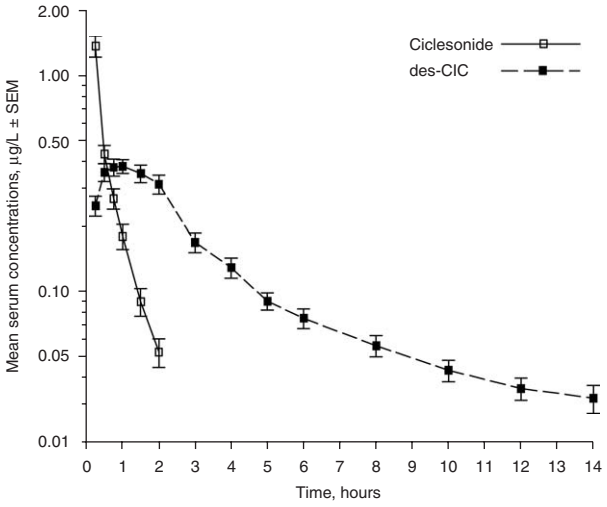

Figure 6 Mean (SEM) serum concentrations of ciclesonide and the active metabolite, des-CIC, in 12 patients with asthma after inhalation of ciclesonide 320 μg ex-actuator (equivalent to 400 μg ex-valve). SEM = standard error of the mean; des-CIC = desisobutyryl-ciclesonide.

Table 5 Concentration of ciclesonide and des-CIC in mouth-rinsing solution after a single inhalation of ciclesonide 320 μg*.

Concentration	Unit	Mean ± SD
Ciclesonide	μg/L (nmol/L)	118.7 ± 57.0 (219.5 ± 105.5)
des-CIC	μg/L (nmol/L)	18.6 ± 13.0 (39.5 ± 27.5)
Ciclesonide plus des-CIC	nmol/L	259.0 ± 129.5
des-CIC (molar basis)	%	14.9 ± 4.9

SD = standard deviation; des-CIC = desisobutyryl-ciclesonide.
*Ex-actuator (equivalent to 400 μg ex-valve).

Table 6 Pharmacokinetic characteristics of ciclesonide and des-CIC in serum after inhalation of a single dose of ciclesonide 320 μg*.

Pharmacokinetic characteristic	Mean ± SD	
	Ciclesonide	des-CIC
$AUC_{(0-inf)}$, μg. h/L	0.68 ± 0.26	1.87 ± 0.66
C_{max}, μg/L	1.36 ± 0.53	0.41 ± 0.11
T_{max}, h	0.25 ± 0.00	0.94 ± 0.39
$t_{1/2}$, h	0.57 ± 0.08	6.02 ± 1.55

des-CIC = desisobutyryl-ciclesonide; SD = standard deviation; $AUC_{(0-inf)}$ = area under the serum concentration-time curve from 0 to infinity; C_{max} = maximum serum concentration; T_{max} = time to maximum serum concentration; $t_{1/2}$ = terminal half-life of des-CIC and distribution/elimination half-life of ciclesonide.
*Ex-actuator (equivalent to 400 μg ex-valve).

adverse events occurred in 2 patients; each of the 3 events was mild to moderate in intensity. One patient reported peripheral swelling and altered sensation of the left hand during the treatment period, which was considered related to the indwelling cannula. Another patient developed mild nausea after inhalation of ciclesonide that was considered ''likely related'' to the study drug. Symptoms in both patients resolved after treatment. There were no deaths, serious adverse events, or study discontinuations due to adverse events. In addition, there were no clinically relevant changes in vital signs or clinical chemistries during the study.

Discussion

Gamma scintigraphy is a widely accepted method used to assess lung deposition of inhaled substances.[19] The reliability of this method depends on adequate radiolabeling of the formulation. Therefore, before this study was performed, labeled and nonlabeled formulations were compared and there was sufficient evidence that the radiolabel procedure did not alter the particle size distribution of the ciclesonide MDI. Moreover, the serum concentration profiles of ciclesonide and des-CIC were comparable with those obtained in a previous study in which the same dose of nonlabeled ciclesonide aerosol was administered to patients with mild asthma.[20] 2D imaging allows overlap in the deposition of inhaled substances in large and small

airways. However, 3D SPECT eliminates this overlap and enables the spatial distribution of the formulation in the lung to be assessed more reliably.[15] Distinguishing between lung compartments is of relevance for the characterization of formulations in which the targeting of distinct anatomic structures in the lung (e.g., peripheral airways) is important for therapeutic effect.

This study demonstrated that more than 50% of the ex-actuator dose of ciclesonide, delivered via HFA-MDI, was deposited in the lungs of patients with mild asthma. In addition, 3D SPECT imaging revealed that the highest deposition of ciclesonide within the lung occurred in the peripheral regions that contain the small airways and alveoli. Patients inhaled ciclesonide slowly and deeply during this study, and distribution of radioactivity appeared to be uniformly distributed in upper and lower lung fields. In contrast, ciclesonide deposition within the oropharynx accounted for 32.9% of the ex-actuator dose. Furthermore, evaluation of mouth-rinsing solutions showed that there was minimal conversion of ciclesonide to des-CIC in the oropharynx.

The deposition and pharmacokinetics of ciclesonide were evaluated in 12 patients with asthma. Scintigraphic studies typically involve between 8 and 12 subjects; therefore, a cohort of 12 patients provides a valid estimate of mean ciclesonide deposition and its variability between patients. The results of this study are consistent with those of a similar study conducted in 8 healthy volunteers.[10] Similarly, deposition of beclomethasone dipropionate from an HFA-MDI was higher in the lungs compared with the oropharynx in 9 healthy volunteers.[21] A control group with another ciclesonide formulation was not employed in this study only because the HFA-MDI formulation of ciclesonide is in development. Selective deposition of ciclesonide in the lungs rather than the oropharynx is a result of the formulation of ciclesonide and use of the HFA-MDI as delivery device. Because of its physicochemical properties, ciclesonide dissolves in the carrier formulation used in the HFA-MDI and is emitted as an aerosol of small particles, with a mass median aerodynamic diameter of $\sim$1–2 μm,[22] which are able to penetrate the narrow pulmonary airways. High oropharyngeal deposition and low lung deposition are usually observed for MDI products in which the drug is formulated as a suspension of micronized particles. For instance, approximately 75–90% of CFC-MDI-delivered fluticasone propionate and beclomethasone dipropionate, respectively, are deposited in the oropharynx, and the majority of the ICS that reaches the lung may be deposited in the central airways with little peripheral penetration.[21,23] Mometasone furoate, administered via an HFA-227 MDI, achieves lung deposition of 7–25%.[24] An HFA-MDI formulation of beclomethasone dipropionate has been shown to produce higher pulmonary deposition and lower oropharyngeal deposition than a formulation of micronized particles suspended in chlorofluorocarbon propellants.[23] Beclomethasone dipropionate was converted to the active metabolite, beclomethasone monopropionate, in precision-cut slices of rat lung, and $>$90% of beclomethasone monopropionate was further metabolized to pharmacologically inactive beclomethasone.[25]

High pulmonary deposition of ciclesonide, coupled with its localization in the peripheral regions of the lung as demonstrated in the present study, probably contributes to the ability of this ICS to maintain lung function, asthma symptom scores, and rescue medication use in patients with mild asthma.[7] Furthermore, des-CIC possesses additional properties—high affinity for the glucocorticosteroid receptor, high lipophilicity, and lipid conjugation—that promote retention of this ICS within the lung and sustained anti-inflammatory activity.[5,25] These properties combine to produce an ICS that, when administered as a once-daily dose, provides effective control of mild asthma.[7]

Oropharyngeal deposition of an ICS can result in local side effects such as oral candidiasis, dysphonia, and pharyngitis.[26,27] Although this study showed that 32.9% of the ex-actuator dose of ciclesonide was deposited in the oropharynx, oropharyngeal activation of ciclesonide was low because less than 15% of the deposited material recovered in mouth-rinsing solutions corresponded to des-CIC. This is consistent with previous reports that oropharyngeal deposition of ciclesonide is lower than that of budesonide or fluticasone propionate.[28,29]

In addition, ICS deposited in the oropharynx may be swallowed with saliva and absorbed from the gastrointestinal tract into the systemic circulation and, thereby, contribute to the development of systemic side effects such as osteoporosis, growth retardation, skin bruising and thinning, and cataracts.[4] Older ICS such as beclomethasone dipropionate and triamcinolone acetonide demonstrate substantial systemic absorption from the gut.[30] However, PK properties such as low oral bioavailability, high protein binding, and high hepatic clearance[9,31,32] contribute to reduced systemic exposure and the improved safety profile of ciclesonide.[33,34] In a recent study, the incidence of oral candidiasis, hoarseness, and pharyngitis in ciclesonide-treated patients was comparable with placebo and lower than fluticasone propionate.[27] In

addition, a pooled analysis of phase II and III clinical studies demonstrated that the incidence of oropharyngeal side effects was similar to placebo and lower than fluticasone propionate 880 μg in patients treated with ciclesonide (up to 640 μg per day).[35]

In conclusion, this study reports that high deposition and peripheral distribution of ciclesonide in the lung is achieved using an HFA-MDI. Similar results were observed in healthy subjects,[10] suggesting that changes that occur in the pulmonary airways of patients with mild asthma have a minimal effect upon the lung deposition of ciclesonide. Furthermore, reduced oropharyngeal deposition, coupled with minimal activation in the oropharynx, may contribute to the reduced incidence of side effects associated with ciclesonide use. Finally, although the present study was conducted in patients with asthma, these patients only had a mild form of the disease, as evidenced by their near-normal lung function. Future studies should be undertaken to determine whether ciclesonide deposition patterns are similar in patients with moderate or severe asthma.

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