Preclinical Profile of Ciclesonide, a Novel Corticosteroid for the Treatment of Asthma

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Received February 23, 2005; accepted May 2, 2005

ABSTRACT

Ciclesonide is a novel, inhaled corticosteroid under development for the treatment of asthma. Ciclesonide is activated to desisobutyryl-ciclesonide (des-CIC) in the lungs to provide potent anti-inflammatory activity. The investigations herein compared the activity of ciclesonide with fluticasone in animal models to assess efficacy/potency as an airway anti-inflammatory and the comparative side effect potential to consider the therapeutic ratio of each compound. In radioligand binding assays, des-CIC and fluticasone exhibited comparable high-affinity binding to the glucocorticoid receptor, whereas ciclesonide exhibited 100-fold less binding affinity. In the Brown Norway rat model of antigen-induced airway eosinophilia and in a model of Sephadex-induced lung edema, ciclesonide and fluticasone exhibited comparable efficacy. Interestingly, following 7-day intratracheal administration, ciclesonide elicited adrenal involution with a potency that was 44-fold less than fluticasone. Furthermore, ciclesonide was 22-fold less active than fluticasone in eliciting hypoplasia of the femoral growth plate. These data support the concept that ciclesonide acts as a parent compound that, when delivered to the airways, can be transformed into the active metabolite des-CIC, resulting in local high anti-inflammatory activity. Furthermore, ciclesonide possesses equivalent anti-inflammatory efficacy through pulmonary activation with a significantly improved safety profile in preclinical animal models compared with fluticasone.

Inhaled corticosteroids are the most effective prophylactic therapy currently available for the treatment of asthma, particularly in patients with mild-to-moderate asthma and persistent symptoms (Barnes, 1998). Airway inflammation is thought to underlie the increased airway responsiveness seen in asthma (Barnes, 1996), and inhaled corticosteroids reduce airway responsiveness to a variety of direct and indirect stimuli in patients with mild asthma (Henriksen and Dahl, 1983; Vathenen et al., 1991; O’Connor et al., 1992). Steroids are thought to possess this beneficial therapeutic profile principally via their anti-inflammatory properties, and regular treatment has been shown to improve lung function, control exacerbations, and attenuate surrogate markers of airway inflammation such as the percentage of eosinophils in induced sputum (Jatakanon et al., 2000).

Although the currently available steroids (including budesonide, fluticasone propionate, and mometasone furoate) have a reasonable therapeutic ratio due to the removal of the swallowed fraction of the drug by the hepatic metabolism, these drugs can be directly absorbed from the lung mucosa, and therefore systemic effects can often be observed at the higher doses (Barnes, 1998). In fact, the systemic side effects associated with the long-term use of inhaled corticosteroids are still a cause for concern. These side effects include suppression of the hypothalamic-pituitary-adrenal (HPA) axis, osteoporosis and reduced bone growth in the young, opportunistic infections, behavioral alterations, disorders of lipid metabolism, oral candidiasis, and glaucoma (Schäcke et al., 2002). Therefore, a major challenge for the pharmaceutical industry is the development of “safer” steroids with an improved therapeutic window (Belvisi et al., 2001a).

Ciclesonide is a new inhaled corticosteroid currently under clinical development for the treatment of asthma. It is a nonhalogenated ester parent compound that is converted in the lung by esterases to form the active metabolite desisobutyrly-ciclesonide.
tory agent in standard animal models of eosinophilic inflammation compared with fluticasone. Furthermore, animal models were configured to examine the systemic side effect profile of ciclesonide compared with fluticasone. In particular, effects on adrenal involution were measured, and decreases in the femur growth plate width were used as a measure of steroid-induced osteopenia.

Materials and Methods

Receptor Binding Studies. Radioligand binding experiments to evaluate the affinity of ciclesonide, des-CIC, and fluticasone for the human glucocorticoid receptor (GR), progesterone receptor (PR), estrogen receptor, and the rat testosterone receptors (TR) were performed as previously described (Eckert and Katzenellenbogen, 1982; Schlecte et al., 1982; Schilling and Liao, 1984; Sheen et al., 1985; Steiner and Wittliff, 1985). In each experiment, the respective reference compound was tested simultaneously at a minimum of eight concentrations in duplicate to obtain a competition curve to validate the experiment.

Assessment of Serum Protein Binding. Serum protein binding of 
\(^{14}C\)ciclesonide (10, 50, 100, 1000, and 10,000 ng/ml) and des-CIC (0.5, 5.0, 25, 100, and 500 ng/ml) was determined in Sprague-Dawley rats. Free and bound drug was separated by ultrafiltration (Centricon 100, Millipore Corporation, Billerica, MA) and quantified by scintillation counting.

Brown Norway Rat Model of Antigen-Induced Airway Inflammation. For all in vivo experiments, compounds were prepared as suspensions by grinding and sonicating the solid in 0.5% methyl cellulose/0.2% Tween 80 in saline. UK Home Office guidelines for animal welfare based on the Animals (Scientific Procedures) Act of 1986 were strictly observed.

Brown Norway male rats (250–300 g) were sensitized on experiment days 0, 12, and 21 with ovalbumin (100 μg i.p.) administered with aluminum hydroxide adjuvant (100 mg i.p.). Each day, between days 27 and 30, rats were challenged (once per animal) with inhaled antigen aerosol (10 g/l, 30 min). Rats were anesthetized with halothane (4% in O₂, 3–5 min) 24 and 1 h before antigen challenge to allow intratracheal instillation of a test compound or vehicle. Rats were sacrificed with sodium pentobarbione (200 mg/kg i.p.) 24 h after antigen challenge followed by cannulation of the trachea. Cell influx into the airway lumen and lung tissue was quantified as previously described (Underwood et al., 1997, 2002).

Sephadex-Induced Lung Edema in the Sprague-Dawley Rat. Sephadex was made up in sterile saline (10 mg/ml) and allowed to swell for at least 3 days at room temperature. The test compounds were administered intratracheally 24 h before Sephadex administration and concomitantly with intratracheal administration of Sephadex (5 mg/kg) under halothane anesthesia (4% in oxygen for 3 min). The rats were sacrificed with pentobarbione sodium (200 mg/kg i.p.) 24 h after Sephadex administration; body weight was recorded followed by the removal of the heart and lungs en bloc. Next, the lungs were excised, and determination of wet lung weights along with correction for 100 g of initial body weight was performed as previously described (Belvisi et al., 2000; Haddad et al., 2002).

Osteopenia of the Femoral Growth Plate in the Sprague-Dawley Rat. The glucocorticoids were administered daily by the intratracheal route for 7 days under halothane anesthesia (4% in oxygen for 3 to 4 min). The adrenal glands and thymic glands were then removed and wet weights determined and corrected for 100 g of initial body weight. The dose causing a 25% reduction (ED\(_{25}\)) in adrenal weight and 50% reduction in thymic weight (ED\(_{50}\)) was determined. The left femur was removed with head intact in the acetabulum by cutting through the pelvic girdle and through the femur shaft above the knee joint as previously described (Belvisi et al., 2001b). The effective dose causing a 20% inhibition of growth plate width (ED\(_{20}\)) compared with the vehicle control group was determined for each compound.

Materials. Estrogen receptor, PR, and TR binding assays (study reference number 992014) were performed by Cerep (L'Evescaut, France). The GR binding assay was performed by Panlabs (Taipei, Taiwan). Fluticasone propionate was synthesized by the Chemistry Department, Aventis Pharma (Dagenham Research Centre, Essex, UK). Ciclesonide and des-CIC were synthesized by Altana Pharma (Konstanz, Germany), and all other materials were purchased from Sigma Chemical (Poole, Dorset, UK), except for aluminum hydroxide from Prolabo (Fontenay, France), sodium pentobarbione (Euthatal), and halothane from Rhône Merieux (Harlow, UK). RPMI 1640 and fetal calf serum was obtained from Invitrogen (Carlsbad, CA). Sephadex G-200 was purchased from Pfizer, Inc. (Täby, Sweden). Carboxymethyl-cellulose (sodium salt), Paranax extra paraffin wax, xylene, acid fuchs, and Alcian Blue 8GX were supplied by BDH Merck (Lutterworth, UK). Neutral buffered formalin (10%) was supplied by Surgipath Europe (Peterborough, UK). Citric acid and formic acid were supplied by Sigma-Aldrich (Gillingham, Dorset, UK). Saline (0.9% w/v) was obtained from Fresenius (Bad Homburg, Germany). Hematoxylin and eosin Y were prepared stains from Thermo Electron Corporation (Waltham, MA).

Results

Receptor Binding Studies. des-CIC and fluticasone fully inhibited \(^{3}H\)dexamethasone binding with a 20- to 30-fold higher binding affinity for the human GR than dexamethasone. The active metabolite des-CIC was about 100-fold more potent than the parent compound ciclesonide (Table 1; Fig. 1). des-CIC exhibited a similar binding affinity for the human GR compared with fluticasone, suggesting that des-CIC is an equally potent

<table>
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<tr>
<th>Binding affinities of ciclesonide, des-CIC, and fluticasone for the human glucocorticoid receptors</th>
<th>K(_{50})</th>
<th>K(_{i})</th>
<th>nH</th>
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<td>Test compounds</td>
<td></td>
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<tr>
<td>Ciclesonide</td>
<td>210</td>
<td>37</td>
<td>0.85</td>
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<tr>
<td>des-CIC</td>
<td>1.75</td>
<td>0.31</td>
<td>0.506</td>
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<td>Fluticasone</td>
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<td>0.444</td>
</tr>
<tr>
<td>Reference compound</td>
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<td>6.7</td>
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analysis of the competition curves. The equilibrium inhibition constants (binding) and Hill coefficients (concentration causing a half-maximal inhibition of control-specific bind-

Fig. 1. Binding characteristics of ciclesonide, des-CIC, and fluticasone for the human glucocorticoid receptor. The compounds were tested in the presence of the protease/elastase inhibitor phenylmethylsulfonyl fluoride (0.6 mM) at 10 concentrations ranging from 0.3 nM to 10 μM in duplicate to obtain competition curves against radiolabeled dexamethasone. The specific radioligand binding to the receptors is defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabeled ligand. Results are expressed as a percentage of control-specific binding and as a percentage inhibition of control-specific binding obtained in the presence of the test compounds. IC50 values (concentration causing a half-maximal inhibition of control-specific binding) and Hill coefficients (nH) were determined by nonlinear regression analysis of the competition curves. The equilibrium inhibition constants (Kd) were calculated according to the Cheng-Prusoff equation [\( IC_{50} = IC_{50}^0 \frac{1 + L/K_d}{L} \] where L = concentration of radioligand in the assay and \( K_d \) = affinity of the radioligand for its receptor).

Protein Binding Data. The in vitro protein binding results of ciclesonide and des-CIC when expressed as the mean percentage of drug bound to serum and plasma proteins, respectively, was high. The extent of protein binding in the rat was 98.6 to 98.9% (for ciclesonide) and 96.86 to 97.65% (for des-CIC). No apparent saturation of protein binding was observed in the concentration range of 10 to 10,000 ng/ml ciclesonide and 0.5 to 500 ng/ml des-CIC.

Brown Norway Rat Model of Antigen-Induced Airway Inflammation. Bronchoalveolar lavage (BAL) revealed a significant influx of eosinophils into the airway lumen after antigen challenge (Fig. 2A). Eosinophilia was suppressed by both ciclesonide and fluticasone in a dose-related manner. The ED50 values for ciclesonide and fluticasone were 0.75 and 0.095 mg/kg i.t., respectively. Antigen challenge also resulted in a significant accumulation of eosinophils in the lung tissue (Fig. 2B). Both ciclesonide and fluticasone significantly inhibited this accumulation in a dose-related fashion. The ED50 values for ciclesonide and fluticasone were 0.49 and 0.068 mg/kg i.t., respectively, and were within 10-fold from each other. The efficacy of both ciclesonide and fluticasone at inhibiting BAL and lung tissue eosinophilia was complete.

Sephadex-Induced Lung Edema in the Sprague-Dawley Rat. Sephadex instillation evoked a significant edema response in the lung, which represented a 29.6% increase in wet lung weight, \( P < 0.01 \). Both ciclesonide and fluticasone significantly inhibited this increase in wet lung weight in a dose-dependent manner. The ED50 for ciclesonide and fluticasone were within 10-fold of each other (0.72 and 0.08 mg/kg i.t., respectively) (see Fig. 3).

Seven-Day Treatment Side Effect Model in the Sprague-Dawley Rat. Both ciclesonide and fluticasone produced a dose-dependent decline in body weight gain. The dose of ciclesonide (0.01–10 mg/kg/day) that inhibited the gain by 50% (ED50) was 0.2 mg/kg/day. In contrast, the ED50 for fluticasone (0.01–1 mg/kg/day) was 0.02 mg/kg/day. Rats receiving 10 mg/kg/day of fluticasone were culled prior to endpoint assessment due to excessive weight loss (>20% initial body weight).

Adrenal and Thymic Involution. Decreases in adrenal weight were both dose-dependent and significant for both compounds (see Fig. 4). Fluticasone produced an apparent reduction at doses as low as 0.01 mg/kg/day. The dose of fluticasone causing a 25% reduction in adrenal weight (ED25) was 0.070 mg/kg/day (i.t.). In contrast, ciclesonide produced no adrenal involution until doses above 0.10 mg/kg/day. The ED25 was 3.11 mg/kg/day (i.t.). Both ciclesonide and fluticasone produced decreases in thymic weight. The dose of ciclesonide that decreased thymic weight by 50% (ED50) was 0.32 mg/kg/day. In contrast, the ED50 for fluticasone was 0.05 mg/kg/day. Thus, compared with fluticasone, ciclesonide was 44.4-fold less potent at inducing adrenal involution and 6.4-fold less potent at inducing thymic involution.

Femoral Head Histology. Femur growth plate width changes from control with steroid treatment are shown in Figs. 5 and 6. A dose-related decrease in growth plate width was observed with fluticasone treatment resulting in a significant reduction compared with control at all doses (\( P < 0.01 \)). Maximal response was at 0.1 and 1.0 mg/kg/day (29 and 31% inhibition, respectively, with ED50 0.04 mg/kg/day). Ciclesonide treatment also produced a dose-dependent decrease in growth plate width. Effects began at a dose of 0.1 mg/kg/day (\( P < 0.01 \)). Maximal inhibition was 23% at 10 mg/kg/day (ED50 0.87 mg/kg). Some reduction of osteogenic effect was indicated at the 10-mg/kg/day dose (21%). Thus, ciclesonide was 22-fold less potent than fluticasone at decreasing bone growth.

Morphology of the growth plate following administration of 0.1 and 1 mg/kg/day fluticasone showed significant resorption within the metaphyses (osteoclast action bordering the hypertrophic zone) and cellular hypoplasia of the zone of proliferation (Fig. 6). Ciclesonide, which produced a significant reduction of growth plate width, did not appear to present with hypoplasia of the proliferative zone, although an increased resorption within the metaphyses was observed.

Discussion

Glucocorticoids are the mainstay of asthma treatment; however, in many cases, major side effects limit their therapeutic usefulness (Barnes, 1998). Side effects occur most commonly during long-term oral administration of glucocorticoids, due to high systemic exposure. However, even topical therapy can induce not only local (e.g., oral candidiasis) but also systemic side effects (e.g., osteoporosis, HPA axis suppression, growth retardation, cataract formation, and skin bruising and thinning) (Cave et al., 1999; Lipworth, 1999; Lane, 2001).

The effects of the modern, synthetic glucocorticoids are mediated by the GR. In brief, upon glucocorticoid binding the receptor, it translocates to the nucleus where it can bind to a glucocorticoid response element in a target gene promoter.
and initiate gene transcription (a process known as transactivation) (Beato et al., 1989). Negative regulation occurs when activated GR binds to negative glucocorticoid response elements, leading to the discontinuation of gene transcription. Alternatively, the GR, activated by ligand, may interact with other transcription factors preventing an activation of transcription without direct DNA binding (processes known as transrepression) (Heck et al., 1994; Barnes, 1998, 2001). Based on the large number of genes regulated in this way, including proinflammatory genes, a hypothesis was formulated that the transrepression mechanism was largely responsible for GR-mediated anti-inflammatory reactions and that transactivation mediated side effects (Reichardt et al., 1998, 2001; Schäcke et al., 2002). Evidence to support this hypothesis has been provided by a study investigating the glucocorticoid responsiveness in GR mutated mice (GRdim/dim). A mutation in the GR of these mice prevents dimerization of the receptor and, thereby, the capacity for DNA binding. Interestingly, all DNA-dependent regulatory mechanisms of the GR are disrupted, but the classical glucocorticoid-mediated anti-inflammatory effects were observed in GRdim/dim mice (Reichardt et al., 1998, 2001). In contrast, for several of the side effects, it has been demonstrated that some effects are mediated predominantly via transrepression (e.g., skin atrophy, suppression of HPA axis), whereas others are mediated predominantly by transactiva-
tion (diabetes mellitus, glaucoma) and some (e.g., osteoporosis) are thought to be mediated by both (Scha¨cke et al., 2002). Currently used glucocorticoids cannot discriminate between the two processes.

One approach to synthesize efficacious but safe steroids has focused on physicochemical properties of inhaled corticosteroids that facilitate optimal pharmacological effects while minimizing unwanted side effects. Ciclesonide was developed using this approach. It is a novel inhaled nonhalogenated glucocorticoid that is activated in the lungs through cleavage of C21-ester bond to form an active metabolite, des-CIC, from the parent compound. des-CIC, which has high local anti-inflammatory activity in the lung, is conjugated to fatty acids to prolong anti-inflammatory activity in the lung, is essentially devoid of oral bioavailability, has high protein binding in the systemic circulation, and is rapidly and completely eliminated from the body (Dietzel et al., 2001). Recent data suggest that the oropharyngeal deposition of ciclesonide is only half that of fluticasone with little activation to des-CIC following inhalation from a hydrofluoro-alkane-propelled metered-dose inhaler in asthmatics, suggesting a decreased likelihood of ciclesonide-associated side effects (Richter et al., 2005).

We found that des-CIC and fluticasone exhibited high GR binding affinity with nanomolar concentrations. Ciclesonide was 100-fold less potent than des-CIC in its ability to bind GR, thus confirming the hypothesis that ciclesonide is the parent compound and des-CIC is the active metabolite. Neither des-CIC nor fluticasone bound to the estrogen receptor, PR, or TR to any appreciable extent, indicating high specificity for the GR. In contrast, fluticasone has been shown to be a weak agonist at the PR when evaluated in cell-based functional systems (Austin et al., 2002). The difference between the two studies may be due to the assays employed, i.e., a simple binding assay compared with a functional system that measures downstream events following receptor binding and activation. The similar binding affinities of des-CIC and fluticasone, at least for the human GR, suggest that the anti-inflammatory potency and efficacy of the two compounds may be similar. However, the relative potency of corticosteroids is best assessed in functional in vitro assays of anti-inflammatory activity. In studies of this sort, the active moiety of ciclesonide and budesonide were roughly equipotent at repressing the activity of the proinflammatory tran-

Fig. 3. Effect of ciclesonide and fluticasone on Sephadex-induced changes in wet lung weight in conscious Sprague-Dawley rats. Compounds were administered by intratracheal administration into the airways 24 h before and together with the Sephadex administration. Data are expressed as percentage inhibition of lung weight and presented as mean ± S.E. of eight observations. A sigmoidal fit was obtained for the data, and the effective dose causing a 50% reduction of the maximum (ED50) lung edema was calculated. The statistical significance of differences between group data were determined using the Kruskal-Wallis multiple comparison test followed by a Dunnett’s post test with *P < 0.05 accepted as significant (**, P < 0.01).

Fig. 4. Effect of ciclesonide and fluticasone on adrenal weight following once daily, 7-day intratracheal treatment in Sprague-Dawley rats. Results are shown as the mean ± S.E. of seven to eight observations. The statistical significance of differences between group data were determined using the Kruskal-Wallis multiple comparison test followed by a Dunnett’s post test with *P < 0.05 accepted as significant (**, P < 0.01).

Fig. 5. Histograms illustrating the effect of ciclesonide and fluticasone on femoral growth plate width after 7-day treatment. Histograms depicting image analysis measurements of femoral head growth plate width from histological sections. Data are expressed as the percentage decrease in femur growth plate width following 7-day intratracheal treatment compared with vehicle control. Results are shown as the mean ± S.E. of seven to eight rats. The statistical significance of differences between group data were determined using the Kruskal-Wallis multiple comparison test followed by a Dunnett’s post test with *P < 0.05 accepted as significant (**, P < 0.01).
In this study, ciclesonide completely suppressed antigen-induced lung and BAL eosinophilia in the Brown Norway rat model and Sephadex-induced lung edema. In both models, the efficacy of ciclesonide was identical to that of fluticasone, and the ED50 for ciclesonide was less than 10-fold higher than that of fluticasone. These data are consistent with a recent report describing the activity of ciclesonide in a similar Brown Norway rat model of allergic inflammation (ED50 = 0.7 mg/kg for inhibition of BAL eosinophilia compared with 0.75 mg/kg in this study) (Stoeck et al., 2004). These investigations used an acute treatment with ciclesonide, although inhaled corticosteroids are administered on a chronic basis for optimal anti-inflammatory therapy in clinical practice. Therefore, such small differences in potency between ciclesonide and fluticasone observed here may not be clinically meaningful when ciclesonide is administered daily for effective treatment of persistent asthma. Furthermore, given the lipophilic nature of ciclesonide and des-CIC (Nave et al., 2004) as well as the ability of des-CIC to form lipid conjugates within the lung (properties that prolong residency time and local anti-inflammatory activity), any minor differences in potency between ciclesonide and fluticasone may be effectively negated with chronic therapy. These points are supported by recent investigations in which daily administration for 21 days with ciclesonide inhibited both bronchial hyper-responsiveness and airway inflammation in an allergic asthma model, whereas fluticasone inhibited airway inflammation but not bronchial hyper-responsiveness (Leung et al., 2003). Furthermore, fluticasone caused systemic side effects at higher doses, although there was no effect on body weight or the HPA axis with ciclesonide. These data are consistent with clinical data showing that ciclesonide, dosed for 7 days at a clinically relevant dose, does not significantly impact on the HPA axis (Weinbrenner et al., 2002). It would have been interesting, as part of this study, to investigate the effect of ciclesonide on airway hyper-reactivity. However, we have previously published that airway hyper-reactivity is not evident in this particular Brown Norway allergic rat model (Underwood et al., 2002).

A major aim of this study was to assess the side effect potential of fluticasone and ciclesonide. Inhibition of bone growth is one of the major limitations of steroid usage. The growth plate region of mammalian long bones contains glucocorticoid-sensitive elements within the proliferative zone. Activation of these elements by exogenous steroids leads to hypoplasia of this zone and reduced cell cycling in the growth plate. The long-term physiological consequence of this is a reduction in long bone growth rate. Previous studies in this laboratory have demonstrated that morphometry of the femoral growth plate is a sensitive marker of steroid impact upon bone (Belvisi et al., 2001b). In these studies, we assessed steroid-induced osteopenia of the femoral growth plate and adrenal involution in the Sprague-Dawley rat as indicators of steroid-sensitive biomarkers indicative of side effect potential. Ciclesonide was found to be 44- and 22-fold less potent than fluticasone at eliciting adrenal involution and hypoplasia of the femoral growth plate, respectively, suggesting that ciclesonide may cause significantly less adrenal suppression than fluticasone. The differences between ciclesonide and fluticasone were apparent but less pronounced when body weight change and thymic involution were considered. The reasons for the discrepancy among these four systemic side effects are unclear but could possibly be due to the varying sensitivities of the tissues to the effects of steroids. The reasons for the reduced side effect profile of ciclesonide compared with fluticasone is not clear but may, at least in part, be due to the extremely high degree of protein binding observed with both ciclesonide and des-CIC (approximately 97–99%) compared with fluticasone (approximately 90%) (Derendorf et al., 1998). These data together with the demonstrated rapid clearance of ciclesonide from the systemic circulation could help to explain the superior therapeutic index described in this article for ciclesonide compared with fluticasone.

In conclusion, this study demonstrates that ciclesonide is a novel inhaled corticosteroid that possesses a combination of physicochemical properties that enables equivalent anti-inflammatory efficacy but a significantly improved safety pro-
file in preclinical animal models compared with fluticasone. The similar binding affinities observed in vitro may explain the similarities between the two compounds in anti-inflammatory potency/efficacy but cannot explain differences in the side effect profile. Other physicochemical characteristics such as on site-activation in the lung, lipid conjugation in the lung, high protein binding, and extensive clearance and elimination are more likely to explain the differences. These data support the proposition that ciclesonide has an improved therapeutic ratio in preclinical studies. Ciclesonide may become an important addition to the armamentarium of anti-inflammatory agents for the treatment of asthma.

References


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