Ciclesonide, a hypotonic intranasal corticosteroid

Hugo Neffen, M.D.,¹ and Mark A. Wingertzahn, Ph.D.²

ABSTRACT

Intranasal corticosteroids (INCSs) are established as the first-line treatment of moderate to severe allergic rhinitis (AR) in both adults and children. Compared with other nasal allergy medications, INCSs are the most effective at providing symptom relief and increasing quality of life. Ciclesonide nasal spray is the most recently approved INCS. The formulation of ciclesonide does not contain benzylalkonium chloride or phenyl ethyl alcohol, excipients that have been associated with reduced mucociliary transport, and unpleasant sensory perceptions. Additionally, ciclesonide has been formulated in a hypotonic suspension that has been shown to optimize intranasal absorption and it has a lower volume of spray compared with most other INCS products. Systemic exposure to ciclesonide and its active metabolite desisobutyryl-ciclesonide is low after intranasal administration. High protein binding (~99%) and rapid first-pass clearance further reduce systemic exposure to the drug. Studies up to 1 year have shown that intranasal ciclesonide does not cause cortisol suppression as monotherapy and does not have an additive effect on the hypothalamic-pituitary-adrenal axis function when administered in combination with inhaled corticosteroids. The efficacy of ciclesonide, 200 µg/day, has been shown in pediatric, adolescent, and adult patients with moderate to severe seasonal AR and perennial AR treated for up to 1 year. Additionally, environmental exposure unit studies have established an onset of action as early as 1 hour after administration. Ciclesonide nasal spray has also been shown to have an acceptable safety profile in patients with AR as young as 2 years of age. Thus, intranasal ciclesonide appears to provide an additional effective treatment option for patients with AR.


Key words: Allergic rhinitis, efficacy, hypertonic, intranasal corticosteroids, nasal allergy medications, quality of life, safety

Allergic rhinitis (AR) is a heterogeneous disorder characterized by nasal itching, sneezing, rhinorrhea, and nasal obstruction, accompanied, in many patients, by allergic conjunctivitis.¹ It is estimated that nearly 20% of the worldwide population suffer from AR.² The incidence of AR has continued to increase and has become a major cause of morbidity, absenteeism, and restricted activity in both children and adults, thereby diminishing affected patients’ quality of life.³,⁴ Intranasal corticosteroids (INCSs) produce greater relief for most of the nasal symptoms associated with AR, are more cost-effective than other therapies, and are indicated as first-line therapy for moderate to severe AR.⁵–⁷

Ciclesonide is a nonhalogenated glucocorticoid that has been developed for the treatment of asthma and AR. R-ciclesonide is activated by intracellular esterases in the upper airways to yield the active metabolite desisobutyryl-ciclesonide (des-cic), which binds to the corticosteroid receptor and thereby exerts its anti-inflammatory potential. Studies have shown negligible oral bioavailability (<1%) and high protein binding (~99%) of ciclesonide and the active metabolite, des-cic, with negligible effects on the hypothalamic-pituitary-adrenal (HPA) axis.⁸–¹⁰ Based on ciclesonide’s prodrug characteristics, high protein binding, high topical anti-inflammatory potential, and favorable benefit-to-risk profile in asthma, it was envisioned that this molecule would be appropriate for further study in the use of AR.

PHARMACOLOGY OF CICLESONIDE

Ciclesonide has been developed as a nasal application for the treatment of nasal symptoms of seasonal AR (SAR) and perennial AR (PAR) in adults and children ≥2 years of age. Ciclesonide is a nonhalogenated glucocorticoid. The molecular formula and in vitro metabolism of ciclesonide to des-cic is displayed in Fig. 1. Although the affinity of ciclesonide to the human glucocorticoid receptor is low, the metabolite des-cic has a 120-fold higher affinity for this receptor than the parent compound¹⁰ and its binding affinity is higher than that of budesonide and similar to other corticosteroids.¹¹–¹⁴ An illustration of in vitro binding affinities for the glucocorticoid receptor of ciclesonide and other corticosteroids is shown in Fig. 2. Preclinical evidence derived from studies using the use of human nasal epithelial cells indicated that although the concentration of ciclesonide decreased over

---

From the Respiratory Medicine Unit, Children’s Hospital “Orlanda Alassia”, Santa Fe, Argentina, and ¹Nycomed GMBH, Florham Park, New Jersey. H.E. Neffen has received research grants, and is a consultant and/or speaker for Nycomed. M.A. Wingertzahn is an employee of Nycomed. Supported by Nycomed. Address correspondence and reprint requests to Hugo Neffen, M.D., Respiratory Medicine Unit, Children’s Hospital “Orlanda Alassia,” Santa Fe S3000CII, Argentina. E-mail address: hugoneffen@arnet.com.ar

Copyright © 2010, OceanSide Publications, Inc., U.S.A.
time, the concentration of des-cic remained near steady-state levels up to 24 hours postincubation. Moreover, these data showed that des-cic reversibly formed fatty acid conjugates that served as a slow-release depot for the active metabolite within the nasal tissue. These findings indicate that the active metabolite is present for at least 24 hours in nasal epithelia and thus supports once daily administration.\textsuperscript{15,16}

Ciclesonide, when administered intranasally, shows negligible absorption into systemic circulation. In three separate studies conducted in patients as young as 2 years of age involving administration of ciclesonide nasal spray at doses up to 800 $\mu$g/day, the majority of serum samples contained undetectable levels of ciclesonide and des-cic.\textsuperscript{17–19} More importantly, no subject had detectable serum levels of ciclesonide or des-cic at any time point after administration of the recommended dose of 200 $\mu$g/day of ciclesonide nasal spray despite the use of a sensitive assay.\textsuperscript{17} These pharmacokinetic findings indicate that the administration of ciclesonide nasal spray at recommended doses will result in negligible serum concentrations of ciclesonide and its active metabolite (des-cic) in adult and pediatric populations.

The plasma protein binding of the active des-cic metabolite in humans is high ($\sim 99\%$) and is not affected by other pharmaceuticals such as warfarin and salicylic acid.\textsuperscript{9} In vitro studies have shown that ciclesonide is metabolized to des-cic by intracellular esterases, which have negligible potential for drug–drug interactions. The systemic metabolism of des-cic occurs within the liver via the cytochrome P CYP3A4 pathway. Experiments, to date, have not found that des-cic interferes with the ability of CYP450 enzymes to metabolize other drugs.\textsuperscript{20} Pharmacokinetic interaction studies conducted with erythromycin (a substrate of CYP3A4) provided no evidence for drug–drug interactions with inhaled ciclesonide \textit{in vivo}.\textsuperscript{21} However, in a separate study, the concomitant administration of inhaled ciclesonide with orally administered ketoconazole, a known inhibitor of CYP3A4, resulted in approximately a 3.5-fold elevation in the area under the curve (AUC) for des-cic blood levels. Taking into consideration that the intranasal dose of ciclesonide has extremely low systemic availability, clinically relevant drug interactions are unlikely after intranasal ciclesonide administration.

In summary, ciclesonide and des-cic have pronounced anti-inflammatory properties due to specific and long-lasting interactions with the glucocorticoid receptor. From a pharmacokinetic perspective, the low oral bioavailability, high clearance, high protein binding, and lack of drug–drug interaction potential provide a good safety profile for ciclesonide nasal spray. The tissue-specific conversion of ciclesonide to des-cic, after intranasal administration, high receptor affinity of des-cic, and long retention of the active metabolite...
des-cic in the nasal tissue caused by reversible lipid conjugation provides a good efficacy profile for the drug.

FORMULATION ASPECTS OF INTRANASAL CICLESONIDE

Unlike some currently available INCS preparations intranasal ciclesonide does not contain benzylalkonium chloride or phenyl ethyl alcohol, excipients that have been associated with reduced mucociliary transport, rhinitis medicamentosa, and unpleasant sensory perceptions, respectively. Ciclesonide is formulated in a hypotonic suspension and has a lower volume of spray (70 μL/actuation) compared with most other currently available INCS products, which are formulated in isotonic suspensions.

This formulation decision was based, in part, on the prodrug characteristics of ciclesonide and also to increase retention time of the corticosteroid in the nasal cavity. By modifying the osmotic pressure, it was hypothesized that this would increase the absorption of the aqueous phase of the suspension. This, in turn, may result in decreased retro-drainage into the esophagus and increase the interaction of ciclesonide with the nasal mucosa and thus ultimately increase absorption of ciclesonide across the nasal mucosa. When a hypotonic suspension is administered intranasally, the difference in osmolarity between the suspension and the nasal mucosa causes water molecules to rapidly diffuse into the nasal mucosa. Increased viscosity and adherence of the suspending agents resulting from loss of water from the suspension then delays mucociliary clearance of the corticosteroid and increases the local drug concentration on the nasal mucosa. In contrast, it is believed that water droplets in an isotonic suspension slowly diffuse along with the drug into the nasal mucosa and thus more is cleared from the nasal mucosa into the esophagus.

Preclinical studies conducted in rabbits have indicated that when ciclesonide is delivered as a hypotonic suspension to the nasal mucosa, there is enhanced uptake of ciclesonide, a higher intracellular concentration of the parent and active metabolite, and longer retention of the active metabolite compared with when ciclesonide is suspended and administered in an isotonic medium. The intracellular concentrations of ciclesonide and des-cic administered in a hypotonic versus isotonic formulation are displayed in Fig. 3. Preclinical data have also shown that there is reduced retrograde drainage when ciclesonide is administered in a hypotonic versus isotonic suspension. Thus, the clinical development program for ciclesonide nasal spray for use in AR was based, in part, on these formulation considerations in addition to the favorable pharmacologic properties of ciclesonide.

CLINICAL STUDIES WITH INTRANASAL CICLESONIDE IN ADULTS

Fourteen well-controlled studies investigating the safety, efficacy, pharmacokinetic, and pharmacodynamic profile of ciclesonide nasal spray have been conducted in healthy normal volunteers as well as patients with AR. Of these studies, 10 have assessed the safety, efficacy, pharmacokinetic, and pharmacodynamic profile of ciclesonide nasal spray.

One phase 1 study that was conducted in healthy volunteers and asymptomatic SAR patients evaluated the safety and tolerability of repeated intranasal doses of ciclesonide (50–800 μg/day) given for 14 days. These data showed that serum ciclesonide and des-cic values were close to or below the threshold of detection regardless of administered dose. Additionally, these data showed no appreciable differences in serum or urinary free cortisol levels between the different drug dose groups.
A phase 2 dose range–finding study was conducted in patients with SAR. Ciclesonide nasal spray at doses of 25, 50, 100, or 200 μg/day was administered once daily for 14 days in patients allergic to mountain cedar pollen. Intranasal ciclesonide administration at doses up to 200 μg/day was associated with statistically significant improvements in nasal symptom relief compared with placebo (Fig. 4). Although statistically significant differences were not observed between the two highest doses of intranasal ciclesonide, the 200-μg/day dose of intranasal ciclesonide was numerically superior to the 100-μg/day dose. The two lowest doses of intranasal ciclesonide (25 and 50 μg/day) did not achieve statistically significant differences from placebo for the primary efficacy measure. The results from this adult dose-finding study indicate that the 200-μg/day dose of ciclesonide will provide a robust and consistent effect in the treatment of AR.

Data from the 14-day, phase 2 dose range–finding study in patients with SAR was confirmed by the 28-day phase 3 pivotal SAR study. The results of this trial, like those obtained from the phase 2 study, showed that once-daily intranasal administration of ciclesonide, at a dose of 200 μg/day, was effective for the treatment of SAR, with a statistically significant improvement from baseline relative to the placebo group in the primary efficacy variable (average of the morning and evening reflective TNSS over days 1–14). Both studies, conducted during mountain cedar season in Texas, showed a similar magnitude of effect (0.82 for the phase 2 dose ranging study and 0.90 for pivotal phase 3 SAR trial), thus establishing a consistent effect of ciclesonide nasal spray above that produced by the vehicle alone in improving the symptoms associated with SAR when administered at 200 μg/day.

The effectiveness of ciclesonide nasal spray in patients ≥12 years old was extended into a PAR population in a pivotal phase 3 study. In this 42-day trial, ciclesonide nasal spray at a dose of 200 μg/day produced a greater reduction from baseline in the average of the morning and evening reflective TNSS compared with placebo. This finding was additionally supported by data for the key secondary efficacy variables. Although the magnitude of the treatment difference obtained in this PAR study was smaller than the effect size seen in the two SAR studies, this was not unexpected because the baseline symptom severity in PAR trials is typically lower than observed in SAR trials.

The adverse events (AEs) from these trials were consistent with those that would be expected in patients with AR or in patients receiving topical corticosteroids. AEs from controlled clinical trials that were 2–6 weeks in duration in patients ≥12 years of age with SAR or PAR are displayed in Table 1.

One long-term, 52-week, randomized, double-blind, placebo-controlled, trial in patients ≥12 years old with PAR was conducted with ciclesonide nasal spray. The primary objective of this study was to show the long-term safety of ciclesonide (200 μg), applied as a nasal spray once daily in adolescent and adult patients. Secondary objectives were to evaluate efficacy and quality of life in patients using ciclesonide nasal spray. Most AEs observed in this study were reported with similar frequency in both treatment groups with events of the upper respiratory tract and nasopharyngitis being among the most frequently reported, as might be expected in a study of an ~1-year duration. These events were reported by a higher proportion of patients treated with placebo than with ciclesonide. AEs that were considered likely or definitely related to ciclesonide nasal spray and reported at an incidence of ≥1% of patients included epistaxis, nasal discomfort, and headache; AEs that are commonly seen in AR patients or with topical corticosteroid administration. Most importantly was that the AE profile over the 52-week treatment period was similar to the AE profile in trials of shorter duration. It is important to note that in this study, no patients experienced nasal septal perforation or a nasal ulcer with ciclesonide nasal spray.

Table 1 Adverse events from controlled clinical trials 2–6 wk in duration in patients ≥12 years of age with seasonal or perennial allergic rhinitis

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ciclesonide Nasal Spray, 200 μg Once Daily (n = 544; %)</th>
<th>Placebo (n = 544; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Ear pain</td>
<td>2.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

![Figure 4](image_url)
With respect to other safety assessments, only small changes from baseline values were observed for either morning plasma cortisol or 24-hour urinary cortisol excretion with no evidence for a change in effect during treatment for up to 1 year. Additionally, changes in intraocular pressure and lens opacifications were similar in both ciclesonide and placebo-treated groups. These results were reassuring and indicate that long-term treatment with ciclesonide is unlikely to have any detrimental effects on the eye.

It is important to mention that this trial is the only one that the authors are aware of that assessed long-term efficacy in a blinded fashion over the entire year-long treatment period. These data showed that the TNSS decreased to a greater extent in the ciclesonide versus placebo group \(p < 0.001\) over the entire treatment duration. An appreciable treatment difference of 0.5 was observed within the 1st week of treatment with ciclesonide nasal spray \(p < 0.001\) and was maintained over every 4-week interval during the entire treatment period \(p = 0.044\). A display of the by-week efficacy results of this study can be found in Fig. 5.

The onset of action of 200 μg/day of ciclesonide nasal spray was assessed as a primary end point in three single dose environmental exposure unit (EEU) studies (unpublished author data). The use of EEUs to determine the onset of action of AR medications were chosen because the use of these are considered by some to be a superior design because outcomes are significantly less variable and more reproducible than park studies or allergen challenge models.

The three studies were replicative in nature and were all conducted as single dose studies in an EEU to assess the onset of action of ciclesonide (200 μg once daily) in the treatment of SAR in adults. The primary efficacy variable was the time to onset of action, which was measured by a difference between the ciclesonide and the placebo groups in the change from baseline in patient-assessed instantaneous TNSS after administration of a single dose of study drug.

All of these trials provide evidence supporting an onset of action within the first 12 hours after ciclesonide dosing. One study showed significant treatment differences in favor of ciclesonide at hour 6 as well as at two additional time points, hours 10 and 12. The second EEU study showed only one time point that had a statistically significant difference in favor of ciclesonide and that was at hour 6 (unpublished author data). The third EEU study showed significant improvements in favor of ciclesonide by hour 1 and this effect was sustained through hour 12, thus establishing the onset of action within 1 hour. Results from these three trials are displayed in Fig. 6.

An inadequately addressed clinical concern with the use of INCSs is the potential for additive systemic effects when administered concurrently with inhaled corticosteroids (ICS). In attempts to answer these questions with respect to intranasal ciclesonide, two studies were designed and conducted to assess the concomitant effects of ciclesonide nasal spray on the HPA axis in patients receiving ICS. The primary objective in both studies was to assess the presence or absence of clinically relevant additive inhibitory effects on the HPA axis when ciclesonide nasal spray was co administered with either orally inhaled hydrofluoroalkane-beclomethasone dipropionate (HFA- BDP), 320 μg, b.i.d. or orally inhaled fluticasone propionate/salmeterol (FP/SAL, 500/50 μg b.i.d.) in male and female patients 18–60 years old with PAR. These studies consisted of a 10-day run-in period during which all patients received HFA-BDP or FP/SAL and placebo nasal spray followed immediately by a 43-day treatment period during which patients received HFA-BDP or FP/SAL with either placebo or ciclesonide nasal spray. At the end of the treatment period, all patients received a 2-mg dexamethasone tablet to demonstrate that further HPA axis suppression was possible. These data showed that administration of either HFA-BDP or FP/SAL decreased mean plasma cortisol AUC\(_{0-24h}\) over the 10-day run-in period. Over the treatment period, the addition of ciclesonide, 200 μg, or placebo nasal spray once daily for 6 weeks resulted in no additional reduction in mean cortisol AUC\(_{0-24h}\), and, furthermore, ciclesonide treatment was shown to be noninferior to placebo in both studies. Decreases in cortisol seen after administration of dexamethasone on the last treatment day indicated that further suppression of the HPA axis by ciclesonide would have been possible. These data suggest that ciclesonide nasal spray, when coadministered with ICS therapy, had no additional inhibitory effect on plasma or urine cortisol when compared with placebo. Thus, patients who require concomitant administration of ciclesonide nasal spray and ICS are unlikely to experience any adverse effects on HPA axis function due to the intranasal treatment.

In summary, results from the adolescent and the adult program with ciclesonide nasal spray have shown that ciclesonide is safe, with an AE rate sim-
ilar to placebo, and effective in adolescent and adult patients with AR with an onset of action as early as 1 hour. Additionally, there were no appreciable effects observed on the HP axis in doses up to 800 μg/day alone or up to 200 μg/day in combination with ICS.

**CLINICAL STUDIES WITH INTRANASAL CICLESONIDE IN CHILDREN**

Four studies have been conducted with ciclesonide nasal spray in pediatric patients 2–11 years of age. These four placebo-controlled studies assessed the use of ciclesonide nasal spray administered once daily in PAR or SAR. Two studies were conducted in 6- to 11-year-old patients and were designed with efficacy as a primary objective. Additionally, two studies were performed in children 2–5 years of age and were designed primarily to assess safety but also included measures of efficacy.

The first pediatric study, conducted in patients 6–11 years of age, was a 12-week randomized, double-blind, placebo-controlled clinical trial in patients with PAR.\(^\text{19}\) The primary objective of this study was to evaluate the efficacy of ciclesonide in pediatric patients (6–11 years old) with PAR. Patients were randomized to one of four treatment arms (placebo or ciclesonide 25, 100, or 200 μg/day). The primary efficacy measure was the average of morning and evening patient/caregiver-reported reflective TNSS over the first 6 weeks of treatment. Spontaneous and elicited AEs were also monitored throughout the duration of the trial as was intraocular pressure and 24-hour urinary free and spot plasma morning cortisol.

The efficacy results from this study showed appreciable, but nonstatistically significant estimated difference, between the ciclesonide, 200 μg/day, and placebo groups of 0.31 (95% CI, −0.1, 0.8; \(p = 0.164\)) for weeks 1–6. With respect to safety, treatment with ciclesonide for up to 85 days did not appreciably change plasma cortisol levels from those recorded at baseline and suggest that there are no clinically meaningful effects of ciclesonide on plasma cortisol levels in this pediatric patient population. Although an attempt was made to assess the plasma concentrations of ciclesonide and des-cic in this trial there were too few values of des-cic that exceeded the sensitivity threshold of the assay. The results from intraocular pressure monitoring showed only small changes throughout the trial that were not indicative of a treatment-related effect. The AE profile of ciclesonide was similar to that seen with placebo in this 12-week study. These data were similar to those seen in adults and adolescents.

A second study was conducted in patients 6–11 years of age with SAR.\(^\text{19}\) The primary efficacy variable in this study was the change from baseline in the average of the morning and evening patient/caregiver-assessed reflective TNSS over the 2-week treatment period.

Spontaneous and elicited AEs were also monitored throughout the trial. The efficacy results showed a decrease from baseline in reflective TNSS over the 2-week treatment period, which was observed in all treatment groups. However, unlike the study conducted in pediatric PAR patients, there was a significantly greater reduction in AR symptoms with the ciclesonide, 200 μg/day, group compared with the placebo group (\(p = 0.040\)) in this study. The lower dose of ciclesonide was not effective. Like in the longer-term study, the AE profile of ciclesonide in this study was similar to that seen with placebo. A display of the most frequently occurring AEs from all pediatric studies conducted in patients 6–11 years of age occurring with an incidence of \(\geq 3\%\) and with a higher frequency in ciclesonide-treated patients are displayed in Table 2.

The third pediatric study was a 6-week study in patients 2–5 years of age with a history of PAR. The primary objective of this study was to evaluate the safety of ciclesonide in pediatric patients aged 2–5 years of age when administered as an intranasal spray formulation at once-daily doses up to 200 μg/day.\(^\text{34}\) The secondary objective was to measure plasma concentrations of ciclesonide and its active metabolite, des-cic, after 6 weeks of treatment. The assessment of plasma concentrations of ciclesonide and des-cic could

![Figure 6. Onset of action of 200 μg/day of ciclesonide in three replicative environmental exposure unit studies.](S34 May–June 2010, Vol. 31, No. 3 (Suppl 1))
Table 2  Adverse events from controlled clinical trials 2–12 wk in duration in patients 2–11 yr of age and older with seasonal or perennial allergic rhinitis

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>6- to 11-yr-Old Patients Overall</th>
<th>Patients, n (%)</th>
<th>2- to 5-yr-Old Patient 6-wk Study</th>
<th>2- to 5-yr-Old Patients 12-wk Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ciclesonide, 200 µg (n = 380)</td>
<td>Placebo (n = 369)</td>
<td>Ciclesonide, 25 µg (n = 34)</td>
<td>Ciclesonide, 100 µg (n = 33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ciclesonide, 200 µg (n = 33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (n = 34)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>—</td>
<td>—</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>—</td>
<td>—</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>—</td>
<td>—</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>—</td>
<td>—</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Platelet count increased</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SBP increased</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (6.6)</td>
<td>21 (5.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>—</td>
<td>—</td>
<td>1 (3.0)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Pharyngitis streptococcal</td>
<td>—</td>
<td>—</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>25 (6.6)</td>
<td>20 (5.4)</td>
<td>2 (6.1)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Increased alk phos</td>
<td>—</td>
<td>—</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Increased body temperature</td>
<td>—</td>
<td>—</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>—</td>
<td>—</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>13 (3.4)</td>
<td>12 (3.3)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; alk phos = alkaline phosphatase.
not be done because there were too few samples that were above the sensitivity threshold of the assay. This is not unexpected given that plasma cortisol levels and urinary free cortisol excretion (corrected for creatinine) showed no appreciable differences between placebo and any dose of ciclesonide. Like in the older pediatric patients, the results from intraocular pressure monitoring showed only small changes throughout the trial and were not indicative of a treatment-related effect. The AE profile of ciclesonide was similar to that seen with placebo.

The fourth pediatric study was conducted as a randomized, double-blind, placebo-controlled, multicenter, parallel-group study of intranasally administered ciclesonide, 200 μg, once daily for 12 weeks, in patients 2–5 years of age with a history of PAR. This was a safety study to assess the effects of longer-term exposure of ciclesonide nasal spray with regard to adverse effects and the HPA axis. Efficacy measures were also collected including the daily morning 24-hour reflective TNSS. Safety results in this study were very reassuring. The incidences of topical AEs were consistent with those expected in pediatric patients with AR using topical corticosteroid therapy. AEs were generally comparable between ciclesonide, 200 μg/day, and placebo treatment. Moreover, the data obtained assessing the effects of ciclesonide nasal spray on the HPA axis, viz., mean morning plasma cortisol, showed an increase in this parameter after both 6 and 12 weeks of treatment with ciclesonide, 200 μg/day, thus suggesting an impact on the HPA axis in these young patients is unlikely.

A display of the most frequently occurring AEs from all pediatric studies conducted in patients 2–5 years of age occurring with an incidence of ≥2% are displayed in Table 2. With respect to efficacy, a statistically significant change from baseline compared with placebo over the entire treatment period was observed in average reflective 24-hour morning TNSS with the 200 μg/day of ciclesonide providing an estimated difference of 0.86 (p = 0.021; 95% CI, 0.13, 1.60) in this study. This effect was observed as early as week 2 and continued throughout the remainder of the treatment period. The effects of ciclesonide nasal spray on the 24-hour reflective TNSS, by week, can be found in Fig. 7. In summary, these data in totality support the favorability of ciclesonide nasal spray with regard to adverse effects and the HPA axis function or ocular health.

SUMMARY

AR is a heterogeneous disorder characterized by nasal itching, sneezing, rhinorrhea, and nasal obstruction. The incidence of AR continues to increase and despite currently available therapeutic options, it continues to be a major cause of morbidity, absenteeism, and restricted activity and is associated with a considerable cost burden to the health care system. Additionally, many patients with AR also have a concomitant diagnosis of asthma. Although patients who have asthma accompanied by AR are often prescribed ICS concurrently with INCSs, the use of these agents in combination is limited by concerns that the systemic effects of these agents may be additive. Thus, an INCS that provides high topical potency in addition to minimal systemic effects when administered alone or concomitantly with ICS would represent an important treatment option for the management of patients with AR.

Ciclesonide is a novel corticosteroid with unique pharmacologic properties. Ciclesonide is a prodrug that becomes biologically active only on conversion by intracellular esterases. The active metabolite of ciclesonide has a high affinity for the glucocorticoid receptor that is comparable with other corticosteroid moieties. Preclinical investigations have shown that the active metabolite (des-cic) resides in the nasal epithelia for up to 24 hours. Unlike currently available INCS preparations that use an isotonic formulation, ciclesonide is formulated in a hypotonic suspension that enhances the delivery of ciclesonide to the nasal mucosa. The formulation of ciclesonide does not contain benzylalkonium chloride or phenyl ethyl alcohol, excipients that have been associated with conferring unpleasant sensory perceptions.

The clinical efficacy and safety profile of ciclesonide, administered as a nasal spray, in patients with AR was established from 14 studies conducted in patients from North America. Efficacy and safety have been observed in patients ≥2 years of age with incidences of topical AEs generally comparable between ciclesonide and placebo treatment with unlikely effects on HPA axis function or ocular health.
In conclusion, the use of ciclesonide in the treatment of AR has been shown to have a favorable benefit-to-risk ratio in patients ≥2 years of age. The results with intranasally administered ciclesonide further suggest that this product will satisfy some of the current unmet needs with INCs therapy and will represent an important treatment option for patients with AR.

REFERENCES

5. Wallace DV, Dykewicz MS, Bernstein DI, et al., and Joint Task Force on Practice; American Academy of Allergy, Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. J Allergy Clin Immunol 122:S1–S84, 2008.