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ORIGINAL ARTICLE

Effect of once-daily generic ciclesonide on exhaled nitric oxide in atopic children with persistent asthma

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Abstract
Background: Ciclesonide (CIC) is an effective inhaled corticosteroid for treating asthmatic children. However, its effect on airway inflammation assessed by the fraction of exhaled nitric oxide (FENO) in children with persistent asthma is virtually unknown. We aimed to assess the effect of once-daily generic CIC, 80 or 160 μg, on FENO, lung function, asthma control and bronchial hyperresponsiveness, in atopic children with persistent asthma.
Methods: This was a 12-week, randomised, double-blind, parallel-group study. Sixty children with mild-to-moderate persistent asthma were recruited. Changes in FENO, asthma control score, lung function (FEV1) and bronchial hyperresponsiveness to methacholine (BHR) were used to assess the effects of both CIC doses. Non-normally distributed variables were log-transformed to approximate normality, and parametric tests were used for comparisons within and between groups at baseline and after 12 weeks of treatment.
Results: In the CIC 80 μg group, FENO decreased from 45.0 ppb (95% CI 37.8–53.7) to 32.7 ppb (95% CI 21.0–47.3) at the end of study ($P = 0.021$), whereas in the CIC 160 μg group, FENO decreased from 47.3 ppb (95% CI 40.4–55.3) to 30.5 ppb (95% CI 24.1–38.7) ($P < 0.001$). The difference between groups in FENO at the end of study was not significant ($P = 0.693$). There was a significant improvement of asthma control with both CIC doses but there was no significant change in BHR or FEV_1 in either group.
Conclusion: Once-daily generic ciclesonide (80 μg or 160 μg), for 12 weeks, is effective to improve airway inflammation and asthma control in atopic children with persistent asthma.

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Introduction

Inhaled corticosteroids (ICSs) are widely recommended as the first-line anti-inflammatory medications for paediatric and adult patients with persistent asthma. Although the effect of different ICSs on asthmatic airway inflammation has been demonstrated in adults, there is much less information regarding childhood asthma, most likely because the invasive methods used in adults to assess the effect of ICSs on airway inflammation are restricted for ethical reasons in children.

FENO is a non-invasive marker of airway inflammation, and it provides useful complementary information for the diagnosis and monitoring of asthma in children.[1–3] Together with other lung function tests, FENO has been employed to evaluate the effects of conventional ICSs such as beclomethasone, budesonide and fluticasone,[4–6] and also of extra-fine corticosteroid aerosols (mass median aerodynamic diameter of $\leq$1.2 μm) such as HFA-beclomethasone and ciclesonide.[7,8]

Ciclesonide (CIC) is safe and effective for improving asthma symptoms, lung function and BHR in asthmatic children, with apparently undetectable systemic effects.[9–14] Although conventional ICSs are effective at reducing airway inflammation as assessed by FENO in asthmatic children,[4–7] there is little information about the effect of CIC on airway inflammation in paediatric patients. The available evidence comes from studies mainly involving adults.[8,15]

The present study was undertaken to determine the effect of once-daily generic ciclesonide, 80 μg or 160 μg, for 12 weeks on the level of FENO, asthma control, lung function and airway responsiveness to methacholine in atopic children with mild-moderate persistent asthma.

Methods

This was a randomised, double-blind, and parallel-group study carried out during the year 2013 at the Hospital El Pino, Santiago, Chile. Sixty children (aged 7–15 years) with mild-to-moderate persistent asthma, positive prick test to one or more common aeroallergens, FENO > 25 parts per billion (ppb) and regular treatment with budesonide or fluticasone during the previous 3 months participated in this study. After a 1-week run-in period when children received the ICS as prescribed at their primary care health centres, they were randomly allocated to receive generic CIC (Disbronc, Neumobiotics, CIPLA) one puff of 80 or 160 μg once daily for 12 weeks, with salbutamol as rescue medication. All aerosols were inhaled using a plastic spacer treated with detergent. The devices containing CIC 80 or 160 μg per actuation were indistinguishable from each other and were numbered according to randomisation; patients, parents and study personnel were blinded until finishing the study.

FENO measurements and asthma control assessments were performed every 30 days. Spirometry and methacholine bronchial challenge were performed at baseline and after 12 weeks of treatment. Tests were carried out on two consecutive days in the same order (first FENO, then spirometry and methacholine); salbutamol was discontinued for 12 h before testing, and ICSs were maintained according to prescription. Participating children were not using long-acting beta-2 agonists, oral corticosteroids, antihistamines, antileukotrienes or theophylline. The primary variable was the change in mean FENO from baseline to the end of the study. Secondary variables were changes in the Asthma Control Test (ACT) score, FEV_1 and BHR to methacholine after 12 weeks of treatment.

On-line single breath FENO measurements (NIOX MINO, Aerocrine AB, Solna, Sweden) were performed according to the ATS guidelines for FENO interpretation.[1] Children were asked to inhale to total lung capacity through the mouthpiece connected to the FENO device and then to exhale for 10 s at 50 mL/s, assisted by visual and auditory cues provided by the device.

Spirometry was performed using a pre-Vent flow sensor with the Medgraphics CPFS/D processing system (Medical Graphics Corp.; St. Paul, MN, USA). The percentage of predicted value for each parameter was calculated according to Knudson's equations.[16] Methacholine bronchial challenge was performed if the FEV_1 was $\geq$ 80% of the predicted value using a modified Cockcroft's method.[17]

A skin prick test for eight common inhalant allergens was performed on the forearm, as was a positive (histamine) and a negative (solvent) control. The following allergens were employed: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, *Alternaria*, a grass mixture, a tree mixture and a weed mixture (Nelco Laboratories, NY, USA). Atopy was defined as a positive reaction (wheal size measuring 3 mm or more after subtraction of the control value) to one or more allergens.

Asthma control was evaluated using the ACT.[18] The questionnaires for children aged <12 and $\geq$12 years were filled in by their parents or the children themselves, respectively, during the medical interview, at baseline and every 30 days until the end of study. Physicians were allowed to clarify parents' and children's doubts as to the meaning of questions. Patients with a score $\leq$19 were considered to have uncontrolled asthma.

The systemic effect of both CIC doses was assessed by measuring cortisol in 24-h urine samples at randomisation and the end of the study; urinary free cortisol was determined by radioimmunoassay with a reference range of 5–50 μg/24 h. Fungal culture of the oro-pharynx was performed in all patients at baseline and at the end of the study for eventual candidiasis induced by inhaled CIC. Height was measured by stadiometry.

This study was approved by the Scientific Ethics Committee, Chilean Ministry of Health, Southern Metropolitan Area of Santiago, Chile. Full informed and signed consent was obtained from all parents.

Statistical analysis

FENO and all positively skewed variables were log-transformed to approximate normality. Parametric tests (independent and paired samples) were used for comparisons between and within groups, at baseline and at the end of the study; the results of log-converted variables are presented as back-transformed values (i.e., geometric means and 95% CIs). Data were analysed using statistical software (SPSS 15.0, Chicago, USA, and MedCalc 13.2, Ostend, Belgium) and $P < 0.05$ was considered statistically