Ciclesonide: A New Inhaled Corticosteroid

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Introduction

Asthma is one of the most common chronic respiratory conditions. The exact etiology of asthma is still unknown but the main state of treatment is to control the underlying airway inflammation. Currently there is no cure for the disease, many adults and children with asthma require prolong treatment of many years to decades. Therefore, it is very important to balance the safety and efficacy in prescribing treatment for asthmatic patients. As described clearly in many asthma treatment guidelines, the goal of asthma treatment is to achieve long term control of asthma symptoms with no significant side effects from their treatment. Inhaled corticosteroids (ICSs) are the cornerstone of asthma treatment and are recommended as daily therapy for persistent asthma. The use of ICSs may be limited by the possible local or systemic side-effects such as adrenal suppression, osteoporosis, and growth retardation in children. Ciclesonide is a new preparation of ICS with unique pharmacology to minimise the possible side-effects of ICS. In this article, we will review the pharmacology, efficacy, and safety profile of this drug for the treatment of asthma.

Pharmacology

Ciclesonide is a new inhaled corticosteroid (ICS) with unique pharmacokinetic and pharmacodynamic properties which differentiate it from other ICSs. Ciclesonide is an inactive pro-drug and it has to be converted to the active metabolites, desisobutyrylciclesonide (des-CIC). The conversion process occurs primarily in the lung. Both ciclesonide and its active metabolite have shown to be highly protein bound thereby reducing the potential for systemic side effects. Ciclesonide is extensively metabolised by the liver to inactive metabolites. Because of this fast pass-metabolism, the systemic bioavailability of ciclesonide after oral ingestion is less than 1%. Furthermore, it has been demonstrated in trials of healthy individuals that conversion of ciclesonide to its active metabolite in the upper oropharynx was extremely low. This property most likely contributes to the low incidence of local side-effect of this drug.

Clinical studies

There have been many clinical studies involving both adults and children with comparison of ciclesonide against placebo and other ICSs. The recommended dose for the maintenance treatment of persistent asthma in adults is 160-320 µg per day. Langdon et al conducted a 12-week placebo-controlled study comparing ciclesonide (80 or 320 µg ex-actuator) given to 360 patients with bronchial asthma and these patients have been previously treated with a constant dose of beclomethasone dipropionate. The results showed that both dosages significantly improve in lung function including peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV1). These results were confirmed with a similar 12-week trial of 329 patients with persistent asthma treated with ciclesonide 160 or 640 µg ex-actuator HFA pMDI.

Buhl et al. conducted a study comparing ciclesonide 160 µg once daily in the evening with fluticasone 88 µg twice daily (ex-actuator HFA-MDI for both drugs) in 529 patients with asthma. The results showed that subjects taking ciclesonide had morning PEF that were similar to those taking fluticasone. There was similar reduction of symptom score and need for rescue medication.

In a recent randomised, double blind, parallel-group comparative study between ciclesonide and fluticasone in 556 children aged 6-15 yrs, both treatments were shown to be effective in improving lung function. There was also significant improvement of asthma symptom score, reduction of use of rescue medication in both treatment groups. Interestingly, the 24hr urine cortisol levels increased significantly from baseline levels by 10% only in the ciclesonide group. Furthermore, there were also recent studies of ciclesonide taken once daily and it was found to be as effective as budesonide taken twice daily. Putting the data of these studies together, it appears that ciclesonide taken once daily is as effective as the other currently available ICSs taken twice daily.

Safety profile of ciclesonide

Long term safety is particularly important for the drugs that patients have to take for long periods of time. For inhaled corticosteroid, one should be considering both local and systemic side-effects. In a study comparing high dose ciclesonide and fluticasone in adult asthmatics with mild-to-moderate persistent asthma, 2.4% of the patients taking ciclesonide (320-640 µg/day) were diagnosed as having oral candidiasis (confirmed by culture) vs 22.0% of the patients taking fluticasone propionate (880 µg/day). The low deposition of ciclesonide in the oropharynx and the low conversion of...
ciclesonide to desisobutyryl-ciclesonide in the oropharynx most likely contribute to such difference.

The important systemic side-effects are adrenal suppression and growth retardation especially when high dose of ICSs are used. Measurement of short-term lower-leg growth rate in children by knemometry is a sensitive measure of systemic activity of topical steroids in children. In a recent study using knemometry to assess lower leg growth in children, it has been demonstrated that both short term lower-leg growth rate and HPA axis function were not affected by treatment with ciclesonide. The effect of ciclesonide on HPA axis function in treatment of mild-to-moderate persistent asthma has been extensively investigated in asthmatics with different degrees of severity. Lipworth et al conducted a study of adults with mild-to-moderate persistent asthma to evaluate the effects of ciclesonide and fluticasone on the hypothalamic-pituitary-adrenal (HPA) axis. Patients were randomised to receive 320 mcg of ciclesonide once daily, 320 mcg ciclesonide twice daily, or 440 mcg fluticasone twice daily for 12 weeks. Assessment of HPA axis included ACTH test and 24 hour urine collection for free cortisol measurement. Only the two groups randomised to receive ciclesonide did not show any significant suppression of ACTH response and urinary free cortisol excretion. Szeffler et al conducted a similar study to assess patients with moderate-to-severe persistent asthma and showed that minimal systemic side effects with a novel inhaled corticosteroid, ciclesonide were not affected by short term lower-leg growth by knemometry. It has been shown to have a very low incidence of local side effects. Multiple studies have also demonstrated that the HPA axis is not significantly suppressed with ciclesonide. Longer term studies are needed to evaluate the possible effects of ciclesonide on bone density of asthmatic patients.

Summary

Inhaled corticosteroids are the mainstay of treatment for persistent asthma in children and adults. Ciclesonide is a new preparation of ICS which can be used in a once-daily regimen. It is a pro-drug requiring conversion to the active metabolite, desisobutyryl-ciclesonide (des-CIC), in the lungs. Because of its unique pharmacology and bioavailability, it has been shown to have a very low incidence of local side effects. Multiple studies have also demonstrated that the HPA axis is not significantly suppressed with ciclesonide. Longer term studies are needed to evaluate the possible effects of ciclesonide on bone density of asthmatic patients.

References