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ORIGINAL ARTICLE

The efficacy of single-high dose inhaled corticosteroid versus oral prednisone treatment on exhaled leukotriene and 8-isoprostane levels in mild to moderate asthmatic children with asthma exacerbation

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Oral prednisone;
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Abstract
Background: The anti-inflammatory effect of high-dose inhaled corticosteroids (ICS) in children with asthma exacerbation is unknown. We aimed to investigate the efficacy of single-high dose ICS versus oral prednisone treatment followed by a course of six day high-dose ICS or oral prednisone (P) treatment on the concentrations of Cys-LTs and 8-isoprostane levels in the exhaled breath condensate (EBC) of children with asthma exacerbation.
Methods: Ninety-four children with moderate–severe asthma exacerbation were evaluated with asthma scores, peak expiratory flow rate (PEF), forced expiratory volume in first second (FEV1) and exhaled Cys-LT and 8-isoprostane levels before and after treatment. EBC was collected from 52 patients before and four hours after treatment with inhaled fluticasone propionate (FP) (4000 μg) or P and after six days of treatment with FP-1000 μg/day or P. Cys-LTs and 8-isoprostane concentrations were determined using a specific immunoassay kit.
Results: Both single high-dose FP ($n = 59$) and p ($n = 35$) treatment resulted in a significant improvement in asthma score ($p < 0.0001$), PEF ($p < 0.0001$), and FEV1 ($p < 0.0001$). Cys-LT concentration in the EBC decreased significantly both after the initial treatment ($p = 0.001$), and at the end of the six-day period in the FP group ($p < 0.0001$). 8-Isoprostane concentration was lower only after six days of treatment with FP-1000 μg/day in the FP group ($p = 0.023$).

Abbreviations: ICS, inhaled corticosteroid; Cys-LTs, cysteinyl leukotrienes; EBC, exhaled breath condensate; PEF, peak expiratory flow rate; FEV_1, forced expiratory volume in first second; ELISA, enzyme linked immunoassay; FP, fluticasone propionate; P, oral prednisone; BAL, bronchoalveolar lavage.

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There was a significant decrease in exhaled Cys-LTs after four hours ($p = 0.012$) and six days of P treatment ($p = 0.018$) in children with asthma exacerbation.
Conclusions: High-dose ICS treatment may be useful in the treatment of children with asthma exacerbation. The effects start as early as after four hours. The suppression of Cys-LTs production contributes to the early effects. Suppression of both Cys-LTs and oxidants may favourably contribute to the effects observed later.

Introduction

Acute exacerbations are common events for asthmatics and continue to be an important health problem. Although international guidelines recommend systemic corticosteroids besides repetitive administration of short acting inhaled bronchodilators in the management of asthma exacerbations, frequent administration may increase the risks associated with systemic corticosteroid treatment in some patients. Even though the use of inhaled steroids during an asthma exacerbation has been proposed as an alternative, there is some concern about its efficacy.[1–3] While some authors have suggested that inhaled steroids seem to act faster than oral steroids on symptoms and airway obstruction,[2,4–6] and the recent Cochrane review of early use of ICS in the emergency department treatment of acute asthma found that there was a reduction from 32 to 17 hospital admissions per 100 patients treated with ICS agents compared with placebo, the same Cochrane review concluded that there was not sufficient evidence to support using ICS agents alone as a replacement for systemic corticosteroid therapy in acute asthma attacks.[7] In addition, its exact mechanism of action in this setting is largely unknown.

In a well designed study about the mechanism of high dose ICS, Belda et al. have shown that high-dose inhaled fluticasone appears to have a faster and stronger effect in reducing sputum eosinophils than oral prednisone and to be as effective as prednisone in reducing plasma exudation, bronchial obstruction, and symptoms in adults with asthma exacerbation.[1]

Inflammation and oxidative stress are essential parts of asthma pathophysiology. Cysteinyl leukotrienes (Cys-LTs) are potent constrictors and pro-inflammatory mediators.[8,9] Higher levels of Cys-LTs have been found in bronchoalveolar lavage (BAL), induced sputum, and in exhaled breath condensate (EBC) of asthmatics, especially in patients with unstable asthma.[8–12] In addition, it has been suggested that Cys-LTs play an important role in airway remodelling. Lex et al.[13] reported that there is a significant relationship between EBC Cys-LTs and reticular basement membrane thickness in endobronchial biopsies in children with asthma. Moreover, it was shown that intravenous montelukast added to standard care in adults with asthma exacerbation produced a significant decrease in airway obstruction throughout two hours.[14]

Eosinophils, neutrophils, macrophages, and mast cells all produce reactive oxygen radicals causing an increased oxidative stress as a feature of airway inflammation in asthma.[15] 8-Isoprostane has been proposed as a good marker of oxidative stress due to its stability, specificity for lipid peroxidation and was shown to increase in asthma.[15,16] Exhaled 8-isoprostane is elevated in asthmatic children, and this increase has not been shown to be affected by inhaled steroid therapy.[12,17,18]

EBC, as a non-invasive and safe technique, has great potential for monitoring airway inflammation and oxidative stress in asthmatic patients.[19–22] In contrast to bronchial biopsy, BAL and induced sputum, EBC collection itself does not affect the airway and therefore can be repeated several times, thus allowing longitudinal follow-up of exhaled markers of airway inflammation as a measure for treatment response.[21] It can be obtained with minimal risk, especially in patients with asthma exacerbation, where contra-indications exist for more invasive techniques. A significant correlation between 8-isoprostane and Cys-LT concentrations both in BAL and EBC have been observed.[23,24]

Exhaled Cys-LT and 8-isoprostane concentrations are increased during an asthma exacerbation[25] and Baraldi et al. have shown that five days of oral prednisolone treatment reduced exhaled Cys-LT and 8-isoprostane concentration in children with an asthma exacerbation.[25]

We aimed to assess the effect of single-high dose ICS versus oral prednisone (P) treatment on both exhaled Cys-LT and 8-isoprostane levels and clinical response in children with moderate–severe asthma exacerbation.

Materials and methods

Subjects

The subjects were children 6–18 years old who had a known history of asthma and who presented with an acute asthma exacerbation. Asthma exacerbation was defined as an increase in symptoms, such as cough, wheezing, shortness of breath or chest tightness, and β2-agonist use.[26] In order to exclude children with lower respiratory tract infections, we did not include children with fever or fine rales with auscultation.

The asthmatic children were evaluated with childhood asthma control test (c-ACT) score and the severity at initial presentation and at follow-up was expressed as ''asthma score'';[27] peak expiratory flow rate (PEF) was evaluated with PEF-meter and forced expiratory volume in first second (FEV_1) measured by a dry spirometer (Sensor Medics, Vmax22, CA, USA). The asthma exacerbation score used in our study is a modification of the asthma score by Qureshi F et al., published by the National Institutes of Health.[28] The interrater reliability of the scoring system, tested in 98 children in the emergency department was good.[27] The