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Effects of inhaled versus systemic corticosteroids on exhaled nitric oxide in severe acute asthma

See Meng Khoo*[,a], T.K. Lim [a]

Division of Respiratory and Critical Care Medicine, National University Hospital, Lower Kent Ridge Road, Singapore 119074, Singapore

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KEYWORDS
Acute asthma;
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Summary
Background: There is a paucity of information on the differential effects of systemic versus inhaled corticosteroids on airway inflammation in patients with acute asthma. This study aimed to evaluate the effects of stopping systemic corticosteroids while maintaining the inhaled corticosteroids (ICS) on airway inflammation, lung function and asthma symptoms in patients who had been discharged from hospital after treatment for severe acute asthma.
Methods: Twenty-four adult patients with severe exacerbations of asthma were treated with both oral and inhaled corticosteroids after discharge from hospital. Oral corticosteroids were stopped after 1 week. Spirometry, asthma quality of life questionnaire (AQLQ) score and exhaled nitric oxide (NO) were measured at discharge, 1 week, and 2 weeks after discharge.
Results: Withdrawal of oral corticosteroids resulted in significant rebound in mean exhaled NO by 11.0 ppb (95% CI, 4.9–17.1 ppb, $p < 0.001$) or 47.7% (95% CI, 22.4–73.1%) despite uninterrupted ICS treatment. The rebound in exhaled NO occurred despite significant improvement in the mean AQLQ score ($p = 0.006$) and frequency of reliever use ($p = 0.003$) and was not associated with significant change in the mean FEV_1 ($p = 0.64$).
Conclusions: In patients discharged from hospital after treatment for asthma exacerbations, withdrawal of oral corticosteroids resulted in increase in exhaled NO levels despite continued ICS treatment.

Introduction

Measurement of exhaled nitric oxide (NO) is a non-invasive test for detection of endogenous inflammatory signals in patient with asthma.[1] Elevated levels of exhaled NO have been documented in patients with asthma.[2,3] Exhaled NO levels are further increased during asthma exacerbations,[4,5] and fall following treatment with inhaled[6] and systemic corticosteroids.[4] Oral prednisolone reduces exhaled NO in

Abbreviations: NO, nitric oxide; FEV_1, forced expiratory volume in 1 s; AQLQ, asthma quality of life questionnaire; ICS, inhale corticosteroids.

* Corresponding author. Tel.: +65 6772 4377; fax: +65 6779 4112.
E-mail address: KhooSM@nuh.com.sg (S.M. Khoo).

[a] Both authors were involved in the planning, data collection, data analysis and writing up of the study.

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infants and young children with wheezing exacerbations.[5] In children with more severe asthma, oral corticosteroids shift their exhaled NO down to the levels of mild-to-moderate asthma with accompanying improvement in lung function.[7] A combination of oral prednisolone and inhaled corticosteroids (ICS) reduces exhaled NO by 65% in children with acute asthma.[8] However, there is an absence of prospective studies that evaluate the differential effects of inhaled versus systemic corticosteroids on exhaled NO, lung function and asthma symptoms in patients with acute asthma.

Sippel and coworkers, in a cross-sectional study, showed that exhaled NO levels were significantly correlated with markers of asthma control such as asthma symptoms, dyspnoea score, use of rescue medication and reversibility of airflow obstruction.[9] Jones and colleagues showed that elevation in exhaled NO levels was a useful early indicator of loss of asthma control following withdrawal of ICS treatment.[10] A similar trend has been observed after withdrawal of leukotriene receptor antagonists.[11] Furthermore, exhaled NO appears to be sensitive to changes in corticosteroids treatment, even in the absence of lung function responses.[12] These findings suggest that exhaled NO may be related to asthma control and corticosteroids treatment, and that serial exhaled NO measurements in individual patients over time may be useful in the adjustment of anti-inflammatory treatment. Although exhaled NO has been used to monitor the effect of anti-inflammatory treatment in asthma[6,13] and asthma exacerbations,[4,12] there is a lack of prospective serial studies of exhaled NO, together with lung function, asthma symptoms and asthma relapse. The utility of serial exhaled NO measurements in patients with acute asthma after completion of systemic corticosteroids treatment, when they are at risk of relapse and re-admissions, has not been studied previously.

The aim of our study was to evaluate the effects of stopping systemic corticosteroids while maintaining the ICS on the exhaled NO levels, lung function and asthma symptoms in patients who have been discharged from hospital after treatment for acute severe asthma.

Materials and methods

Study subjects

Adult patients admitted to the Medical Department of a university hospital with acute exacerbations of asthma were invited to participate in the study. All patients were non-smokers, had prior diagnosis of asthma and had presented with symptoms consistent with acute exacerbations to the Emergency Department. Asthma was diagnosed based upon a history of episodic respiratory symptoms, a prior physician's diagnosis of asthma, the use of inhaled asthma therapy and pulmonary function testing prior to the exacerbation which demonstrated at least 15% improvement in FEV_1 following bronchodilator therapy. Acute exacerbations were defined as increasing symptoms requiring emergency treatment and presentation to the hospital. Ethical approval was obtained from the National Healthcare Group (NHG) Ethics Committee and informed consent was obtained from all study participants.

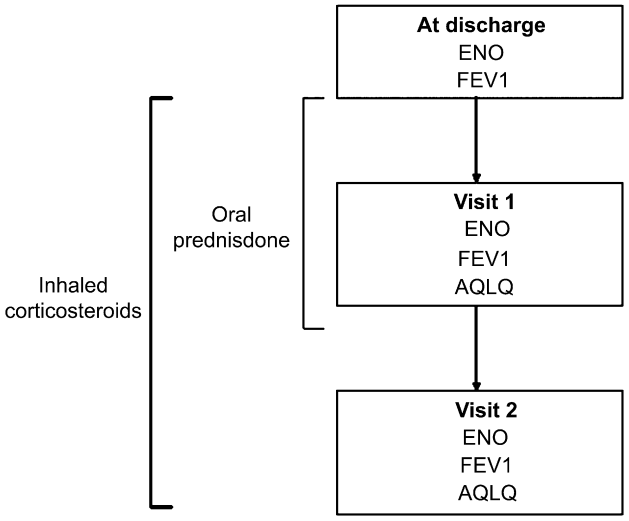

Figure 1 Measurements done at discharge, visit 1 (1 week after discharge from hospital) and visit 2 (2 weeks after discharge from hospital). Definition of abbreviations: ENO = exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 s; AQLQ = asthma quality of life questionnaire score.

Study design

Patients who did not respond adequately to therapy instituted in the Emergency Department were admitted to hospital for inpatient treatment of acute asthma. Research nurse was contacted to screen for eligibility, obtain informed consent and complete clinical asthma questionnaire. During the inpatient period, all patients received standard treatment for acute asthma, which consisted of 5 mg of nebulized salbutamol and 500 μg of ipratropium bromide every 6 h for the first 24 h and systemic corticosteroids in the form of oral prednisolone of 0.5 mg/kg. Patients were also maintained on their usual dose of ICS. Decision to discharge patients from hospital was made by the attending physicians based on symptom resolution and lung function.

On the day of discharge, all patients were continued on ICS and prescribed a non-tapering course of prednisolone of 0.5 mg/kg per day for 1 week. Spirometry and exhaled NO were measured on the day of discharge. Spirometry, exhaled NO and asthma quality of life questionnaire (AQLQ) were measured at visit 1 (1 week after discharge, when the patients had been on both oral prednisolone and inhaled corticosteroids) and at visit 2 (2 weeks after discharge, when the patients had been on maintenance ICS only). Measurements obtained at each visit are shown in Figure 1. Patients were instructed to keep diaries on the frequency of reliever use. All patients were contacted by a research nurse by telephone after hospital discharge to reinforce compliance with asthma medications. They were also contacted monthly for 3 months after hospital discharge to obtain information relating to relapses which required commencement of systemic corticosteroids, increase in maintenance dose of inhaled corticosteroids, unscheduled visits to doctors or hospital admissions.

Exhaled NO level was measured according to the 1999 American Thoracic Guidelines,[14] using a nitric oxide