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A Review of the Role of Inhaled Corticosteroids in the Treatment of Acute Asthma

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Summary: Systemic corticosteroids (CSs) are generally accepted as treatment for acute exacerbations of asthma. In contrast, inhaled corticosteroids (ICs) have been used for the long-term management of asthma but are not widely accepted for the treatment of asthma exacerbations. The onset of action of ICs in acute asthma begins in 1 hour. In patients with mild to moderate exacerbation, administration of high-dose ICs may decrease the need for hospital admission and the number of symptomatic days. *Clin Pediatr.* 2001;40:185-189

Introduction

Acute respiratory obstruction may be associated with a number of specific conditions in infants and children. With approximately 4.8 million children affected in the United States, asthma is the most common chronic disease of childhood.¹ Acute attacks result in 1 to 2 million visits of adults and children to emergency departments (EDs) annually² and represent a common condition treated in the pediatric ED.³ Once treated in the ED, up to 25% of patients relapse within 10 days.⁴

Inhaled corticosteroids (ICs) have been an accepted treatment for chronic asthma in the United States for 20 years. Recent guidelines of the National Asthma Education and Prevention Program recommend the use of ICs as primary antiinflammatory therapy for mild, moderate, and severe persistent asthma.¹ The available preparations in the United States are listed in order of decreasing potency (Table 1). Several recent publications^{5,6} have suggested that ICs may be added to usual emergency department therapy for acute asthma, realizing the goal of faster reduction of airway

obstruction and decreased need for hospital admission.

Corticosteroids in Acute Asthma

The recognition of asthma as an inflammatory disease provides a rationale for the use of corticosteroids (CSs) early in treatment.¹ In a metaanalysis of several randomized, placebo-controlled trials evaluating systemic CSs to treat acute asthma exacerbations, Rowe et al⁵ concluded that oral CSs were beneficial in reducing relapses in the first 7 to 10 days of treatment. However, a recent study suggested that the onset of action of parenteral CSs may be considerably slower than that of ICs.⁶ The effects of parenteral CSs on pulmonary function in this investigation were not apparent before 6 to 24 hours following initiation of treatment in adults and children. In contrast, at a 1-hour assessment time, a small effect was demonstrable with ICs.

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Table 1

INHALED CORTICOSTEROID PREPARATIONS LISTED IN ORDER OF DESCENDING POTENCY

Steroid	Trade Name	Delivery System	Mcg/Puff	
Fluticasone propionate	Flovent	PMDI	44, 110, 220	
		DPI	50, 100	
Budesonide	Pulmicort Turbuhaler	DPI	200	
	Pulmicort Respules	Neb Susp	250, 500 mcg/Vial	
Beclomethasone dipropionate	Beclivent	PMDI	42	
		Vanceril	PMDI	42
		Quvar	PMDI (Autohaler)	40, 80
Triamcinolone acetate	Azmacort	PMDI	200	
Flunisolide	Aerobid	PMDI	250	

DPI = dry powdered inhaler, PMDI = pressurized metered dose inhaler, Neb Susp = nebulized suspension.

Several trials evaluated ICs for acute asthma in adults. In 1 trial when inhaled budesonide (BUD) 1,600 µg/d via Turbuhaler® was added to a nontapering course of prednisone (50 mg/d × 7 d) following discharge from the ED after standard treatment with nebulized β₂-agonist and 50 mg of oral prednisone, high-dose inhaled BUD reduced symptomatic days and need for additional asthma care.⁷ Furthermore, high-dose inhaled fluticasone propionate (FP) (2,000 µg/d) was comparable in efficacy to a tapering course of oral prednisone (starting at 40 mg/d and tapering down by 5 mg every other day for a total of 16 days) for mild exacerbations of asthma.⁸ The administration of inhaled flunisolide (FI) (1,000 µg/dose) in addition to salbutamol (albuterol, 400 µg/dose) in the ED resulted in improvements in peak expiratory flow (pef) and forced expiratory volume in 1 sec-

ond (FEV₁) for FI-treated patients compared with placebo.⁹ The hospital admission rate was significantly higher for patients with asthma duration of 24 hours who received placebo than for patients with a similar duration of asthma treated with flunisolide. Flunisolide (FI) treatment did not alter the hospital admission rate in patients with asthma duration <24 hours as compared with placebo. Patients treated with FI had more rapid resolution of symptoms, which occurred within 2 hours after presentation to the ED.

The addition of ICs to bronchodilator therapy in the ED has been shown to hasten the resolution of acute asthma attacks and reduce hospital admissions. A study by Afilalo, et al¹⁰ reported a randomized study of 15 adults treated at baseline, 30, 60, 120, and 240 minutes with 2,500 mcg of albuterol via metered dose inhaler (MDI) with spacer.¹⁰ One

half of the group was given 1,000 mcg of beclomethasone dipropionate (BDP) and the other half placebo. FEV₁ improved in a similar manner for both groups with an 18% improvement for the BDP-group compared to a 17% improvement for the placebo group at 6 hours. However, only 7% of the BDP group was admitted compared to 19% of the placebo group. Admission criteria were determined by the treating physician. Thus in adults the addition of CSs appears to hasten the resolution of acute asthma attacks.

Studies of inhaled CSs in the management of acute asthma have also included children. A double-blind, intrasubject comparison of inhaled BDP and placebo showed that intermittent high-dose inhaled BDP (750 µg 3 times daily × 5 d) reduced the severity of acute asthma exacerbations in preschool children treated at home at the onset of symptoms.¹¹

A subsequent investigation studied 28 children (age 6–14 years) with mild to moderate asthma treated in the home environment during a 6-month period.¹² During this time the subjects were randomized to receive a regular dose of inhaled corticosteroid 800 mcg twice a day (BDP or BUD) with spacer and increased to 1,600 mcg twice a day given by a separate inhaler with the onset of respiratory symptoms. The extra dose for the treatment of acute asthma exacerbation was delivered by either active drug inhaler or placebo inhaler. In this home-monitored study, there was no significant difference in the groups. The study design, however, did not have the power to determine a significant difference in exacerbation rate. Thus when studied in the home environment, inhaled corticosteroids may offer improvement in symptom management.

Other studies have evaluated the effectiveness of ICs in the Emergency Department setting. Nebulized dexamethasone (1.5 mg/kg) was found to be as effective as oral prednisone (2 mg/kg) in reducing symptoms of acute asthma in children treated in the ED.¹³ More children were discharged from the ED within 2 hours, and fewer required hospitalization with dexamethasone treatment than when treated with prednisone (discharged: 23% vs 7%, $p=0.02$; hospitalized: 21% vs 31%, $p=0.26$).¹³

In a study of 44 children 6 months to 18 years of age with an acute asthma exacerbation, inhaled BUD was compared with placebo as an adjunct to oral prednisone in an ED setting.³ Patients were treated with nebulized albuterol (0.15 mg/kg every 30 minutes for 3 doses and then hourly for 4 doses). After the sec-

ond dose of albuterol, patients were randomized to treatment with 2,000 μ g BUD or placebo, both administered with a nebulizer. A single dose of prednisone 1 mg/kg was administered orally to all patients following the administration of the study drug. Patients receiving BUD had a 20% greater improvement in symptoms that was evident within 1 hour. Furthermore, BUD patients had a lower probability of remaining in the ED or hospital.

In another study,¹⁴ a group of 22 children 6 to 16 years of age with an acute asthma exacerbation received terbutaline (1.25 mg administered either by nebulization or by 1 puff of 0.5 mg/dose Turbuhaler) in the ED. They were then randomized to receive a single dose of 1,600 μ g BUD administered by an inhalation-driven dry powder inhaler (Turbuhaler) or 2 mg/kg prednisolone orally in a double-blind fashion. After discharge from the ED, patients continued the assigned treatment at home and tapered the dose to 400 μ g/d BUD or 0.5 mg/kg per day prednisolone over the next week. This final dose was continued for 1 additional week. Improvements in peak expiratory flow and symptom score at 4 hours were comparable in both treatment groups. An earlier clinical response, as defined by reduced daytime and nighttime cough, was observed within 2 days in children who received BUD. Children treated with prednisolone experienced a small transient decrease in serum cortisol concentration, which was not observed in the children treated with BUD. A short course of inhaled BUD, therefore, was as effective as oral prednisolone in this study.

In a subsequent emergency department study,¹⁵ 80 children (2–12 years of age) with acute ex-

acerbations of asthma received standard therapy consisting of 3 doses of 0.15 mg/kg of albuterol by nebulization. One subgroup received 800 mcg budesonide inhalation suspension (BIS) every 30 minutes and a placebo tablet. The second subgroup received albuterol, placebo, BIS inhalation, and 2 mg/kg of prednisone orally. At the end of the third albuterol treatment, the BIS group had improved oxygen saturation, respiratory rate, and clinical symptoms. Fifty-four percent of BIS patients met criteria for discharge compared to 18% of the prednisone group. A second group of 46 children (5–16 years of age) admitted to the hospital were studied.¹⁶ In addition to standard therapy, 1 group received BIS 2,000 mcg every 8 hours or prednisone 2 mg/kg/day. Over the first 48 hours, there was significant improvement in FEV₁ in the BIS group compared to oral prednisone, but clinical symptoms and oxygen saturations were similar.

Schuh et al¹⁷ reported a double-blind, randomized study comparing a single dose of 2 mg of inhaled fluticasone propionate (FP) given by MDI to a single dose of 2 mg/kg of oral prednisone in 100 children (9 years old, range: 5–17 years) who presented to the emergency department with an acute asthma exacerbation. The average FEV₁ was 46.3 \pm 12.5% in the ICS group and 43.9 \pm 9.3% in the oral steroid group. After 4 hours of treatment, FEV₁ increased by 9.4 \pm 12.5% in the ICs group compared to 18.9 \pm 9.8% in the prednisone group ($p<0.001$). Additionally, 25% of the patients in the ICs group had reduction in FEV₁ at 4 hours, whereas none of the patients in the prednisone group did. Each patient was treated with repeated high-dose beta agonist and ipratropium bro-

mide for the first 140 minutes of the emergency department visit. After discharge the ICs group received 500 mcg FP twice daily plus oral placebo. The prednisone group received 1 mg/kg of prednisone (maximum 40 mg) plus placebo MDI for 7 days. Hospitalization was necessary in 10% of the prednisone group and 31% of the ICs group. None of the patients who were discharged from the emergency department required admissions during the next week. Thus this study would indicate that oral prednisone is more effective than ICs in acute control of an asthma exacerbation and in decreasing hospitalization from the ED.

Conclusions

The mechanism of action of inhaled and oral or parenteral steroid in acute asthma is related to the vasoconstrictive effect in the airway. At the onset of action there is decrease in plasma leak and resultant edema, which may be manifest in 1 hour with inhaled steroid and maximal effect in 3 hours.⁹ The effect of oral or parenteral steroid becomes evident at 6 to 8 hours after the dose.⁹ The local effects may have potential effects to up-regulate sensitivity to β_2 adrenergic receptors, leading to more effective bronchodilation. Doses of oral prednisone (1–2 mg/kg) may lead to mild reduction in cortisol concentrations; however, this is not seen with short-term (<2 weeks) use of ICs.^{9,14}

The data currently available may provide us insight into the possibility of modification of the home management programs to prevent emergency department visits. Patients who are receiving ICs as maintenance therapy may

double or triple their dose with increased asthma symptoms. When emergency room visits are necessary for mild to moderate exacerbations, high-dose inhaled corticosteroid may decrease the necessity for hospital admission. With more severe exacerbations, a single dose of ICs has not been proven to be more efficacious than oral prednisone.¹⁷ The continuation of inhaled corticosteroid after treatment of an acute exacerbation may decrease the need for repeat emergency room visits and subsequent admission to the hospital. Further studies are needed to determine the optimal dose of inhaled corticosteroid, delivery system and duration of therapy. Also, further studies should be done to optimize concurrent therapy with drugs such as leukotriene receptor antagonists, interleukin antagonists, and anti-IgE as complementary therapy in acute exacerbations of asthma.

The studies referenced in this review suggest that increasing the dose of ICs used as maintenance therapy or high-dose ICs in the ED may help prevent hospital admission and decrease the length of asthma exacerbation.

Abbreviations

BIS=budesonide inhalation suspension

BDP=beclomethasone dipropionate

BUD=budesonide

CSs=corticosteroids

DPI=dry powdered inhaler

ED=emergency department

Fl=flunisolide

FEV₁=forced expiratory volume in 1 second

FP=fluticasone propionate

ICs=inhaled corticosteroids

PEF=peak expiratory flow

PMDI=pressurized metered dose inhaler

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