
Oral corticosteroid–sparing effects of inhaled corticosteroids in the treatment of persistent and acute asthma

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Objective: To review the efficacy and safety of inhaled corticosteroids (ICSs) when used to reduce daily oral corticosteroid (OCS) requirements in patients with severe persistent asthma and periodic requirements in patients with acute asthma exacerbations.

Data Sources: Clinical studies of the OCS-sparing effects of ICSs were located by searching MEDLINE databases from 1966 onward using the terms *oral*, *steroid*, and *asthma* in combination with the generic names for each marketed ICS.

Study Selection: Studies reporting on the use of ICSs to reduce OCS requirements in patients with persistent and acute asthma are included.

Results: Clinical study results consistently show that ICSs significantly improve asthma control and reduce OCS requirements among adults, children, and infants with persistent asthma. A dose reduction or complete discontinuation of use of OCSs is possible in most patients without loss of asthma control. ICSs also can control asthma during acute asthma exacerbations and reduce the need for short courses of OCSs. With many ICSs, the reductions in OCS use are accompanied by recovery of hypothalamic-pituitary-adrenal axis function, indicating that the safety of asthma therapy is improved when OCS requirements are decreased with ICSs. Of the available ICSs that may reduce OCS needs, budesonide appears to be the most intensively studied.

Conclusions: ICSs can reduce OCS requirements in adults and children with persistent asthma and during acute asthma exacerbations. The reduced systemic corticosteroid activity associated with ICS treatment improves the overall safety of asthma therapy.

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INTRODUCTION

Recognition of the importance of inflammation in asthma has led to a general acceptance of corticosteroid therapy as the mainstay of treatment.¹ Corticosteroids reduce the severity of asthma symptoms, improve airflow limitation, reduce airway hyperresponsiveness, and decrease the risk and severity of exacerbations.¹ If begun early in the disease, such therapy also may prevent the irreversible airway wall remodeling observed in some patients with persistent asthma.^{2,3}

The earliest corticosteroid therapies involved oral formulations. Long-term exposure to oral therapy, however, can result in serious adverse effects, including adrenal suppression, growth retardation, hypertension, glucose intolerance, Cushing syndrome, cataracts, and osteoporosis.^{1,4–7} Adrenal suppression is particularly problematic, because it is often a consequence of long-term oral corticosteroid (OCS) use, and acute adrenal insufficiency is a medical emergency. Less serious problems include dermal thinning, ecchymosis, tissue edema, and mood swings. Most of these effects are related to the cumulative drug dose.^{1,8}

Consideration of these effects led to the development of inhaled corticosteroids (ICSs), which can be delivered directly into the inflamed airways. Targeted delivery enables therapeutic benefits to be achieved with lower doses and less systemic activity than can be attained with OCSs.⁹ Currently, ICSs are recommended as first-line therapy for all severities of persistent asthma in children and adults.¹⁰ The addition of a long-acting β_2 -agonist to ICS therapy is recommended to achieve asthma control in patients with moderate or severe disease.¹⁰ Long-term OCS use is only suggested for cases of severe persistent asthma that cannot be controlled by ICS and long-acting β_2 -agonist use or when a patient is unable to take inhaled medication.^{1,10} Short-term therapy with OCSs also may be considered in emergency situations when it is necessary to gain immediate initial control of asthma exacerbations.¹¹ Although oral prednisone was more effective than ICS treatment in one study of 68 children 5 years or older with severe acute asthma,¹² several studies support ICS therapy as an effective alternative to OCSs for the management of acute asthma.^{13–16}

Long-term use of OCSs for the treatment of asthma has declined considerably since the introduction of ICSs. However, a substantial number of patients remain dependent on OCSs for long-term symptom control or for short-term management of exacerbations. These patients would benefit from therapies that permit them to minimize or eliminate their use

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of OCSs. This article reviews studies of the efficacy and safety of ICSs when administered to reduce OCS use in adults and children with persistent asthma. Clinical studies cited in this review were located through a search of MEDLINE databases from 1966 onward. A separate search was conducted for each ICS described, using the generic name in combination with the terms *oral*, *steroid*, and *asthma*. Studies reporting the efficacy and safety of an ICS in reducing OCS use in patients with persistent asthma or for the management of acute asthma exacerbations were selected for inclusion.

OCS-SPARING EFFECT OF ICSs

ICSs may reduce the need for OCS therapy either by decreasing OCS requirements in patients receiving long-term oral therapy or decreasing the need for short courses of OCSs to manage exacerbations. This section includes studies examining both forms of OCS-sparing effects in adults and children with persistent asthma (Table 1).

First-Generation ICSs

Beclomethasone dipropionate (Vanceril Inhalation Aerosol, Schering Corp, Kenilworth, NJ), introduced in the United States in 1976, was the first ICS to provide an effective and safe alternative to OCSs. Early short-term (≤ 12 weeks) and long-term studies demonstrated that most OCS-dependent patients given beclomethasone aerosol eventually discontinued use of OCSs or reduced their doses.^{17–20,43–47} However, some patients required high doses of beclomethasone to eliminate their need for OCSs, which increased their risk for adverse events.^{48–50}

Triamcinolone acetonide (Azmacort Inhalation Aerosol, Aventis Pharmaceuticals Inc, Bridgewater, NJ) is another first-generation ICS developed for the treatment of persistent asthma. Early short-term studies demonstrated that triamcinolone aerosol, 800 $\mu\text{g}/\text{d}$, enabled 65% or more of adults with severe persistent asthma to discontinue OCS use.^{51–54} Similar results were obtained in long-term studies,^{21–23} indicating that, as with beclomethasone aerosol, triamcinolone aerosol could have significant OCS-sparing effects in adults with persistent asthma. However, other studies suggested that triamcinolone was less potent than beclomethasone and not as effective at improving lung function and symptom control.^{55,56}

Flunisolide aerosol (Aerobid Inhaler System, 3M Pharmaceuticals, St. Paul, MN) is a third first-generation ICS for adults and children with persistent asthma. Studies with this ICS suggest that, although it has some benefit in reducing OCS requirements, this benefit may not be as pronounced as with other ICSs.^{24–26}

Second-Generation ICSs

Budesonide. Budesonide has been available in many countries as a pressurized metered-dose inhaler (pMDI; Pulmicort pMDI, AstraZeneca LP, Lund, Sweden) for the treatment of persistent asthma in children and adults since 1983. More recently, budesonide was made available in the United States and elsewhere as a chlorofluorocarbon-free dry powder inhaler (DPI; Pulmicort Turbuhaler, AstraZeneca LP, Wilming-

ton, DE) and in a nebulized form (budesonide inhalation suspension; Pulmicort Respules, AstraZeneca LP). Budesonide administered via Turbuhaler has lower oropharyngeal deposition and higher lung deposition (21% to 32%)^{57,58} compared with other ICSs administered via Rotahaler and Diskhaler (9% to 12%)⁵⁷ or chlorofluorocarbon-based pMDIs (4% to 15%).^{57,59} Budesonide inhalation suspension is approved for use in children as young as 12 months in the United States⁶⁰ and 3 months in the United Kingdom.⁶¹

Clinical trials involving adults with severe, persistent, OCS-dependent asthma have shown that budesonide administered via pMDI, Turbuhaler, or nebulizer is effective in reducing OCS requirements. In an early open-label study of patients treated with OCSs for up to 19 years,³² doses of budesonide pMDI were increased stepwise from 200 $\mu\text{g}/\text{d}$ to between 800 and 1,600 $\mu\text{g}/\text{d}$ as prednisolone doses were gradually decreased. After 2 years, 47% of patients had discontinued use of systemic corticosteroids and 29% had reduced their dose by 50% or more.

In a subsequent 6-month, open-label study, patients using inhaled beclomethasone (400 $\mu\text{g}/\text{d}$) and oral prednisolone for asthma control were able to reduce their mean daily OCS dose from 8.3 to 4.2 mg when beclomethasone was replaced by budesonide, 800 μg twice daily, administered via pMDI/spacer.³³ Twenty-eight percent of patients discontinued use of OCSs and 31% reduced their dose by 50% or more.

Another study compared the prednisone-sparing effects of high-dose (800 μg twice daily) and conventional-dose (200 μg twice daily) budesonide administered via pMDI/spacer.³⁴ After the 15-week, double-blind phase, mean oral prednisone doses were reduced by 39% and 54%, respectively, in those patients receiving budesonide, 200 or 800 μg twice daily. Forty-five patients continued in an open-label, 36-week study at the 1,600- $\mu\text{g}/\text{d}$ dose, after which 40% of patients were able to discontinue use of OCSs. In these 3 pMDI studies, asthma control was maintained or improved.

Budesonide DPI also has been proven effective in reducing OCS requirements. In a 20-week randomized study of adults with moderate-to-severe persistent asthma, patients given budesonide, 400 or 800 μg twice daily, significantly reduced their mean daily prednisone dose by 82.9% and 79.0%, respectively, whereas those given placebo reduced their daily prednisone requirements by only 27.3%.³⁹ Oral prednisone use was completely discontinued by 68% of patients who received budesonide, 400 μg twice daily, and by 64% of patients given budesonide, 800 μg twice daily (Figure 1). The percentages of patients discontinuing prednisone use were remarkable given the high mean daily doses of prednisone (approximately 19 mg) required by patients at randomization compared with doses reported in other studies (eg, 10 mg in the study by Noonan et al in 1995,²⁷ 14 mg in the study by Nelson et al in 1999²⁹).

Similar results were obtained from a placebo-controlled study of Japanese adults with moderate-to-severe persistent asthma taking daily oral prednisolone.⁴¹ After 26 weeks, the mean daily OCS dose was reduced by 35% in patients taking

Table 1. Reduction of Oral Corticosteroid Requirements with Inhaled Corticosteroid Therapy

Study	Study population	Treatment	Patients discontinuing OCS use, %	Additional outcomes
Beclomethasone				
Davies et al, ¹⁷ 1977	44 adults	Beclomethasone dipropionate, 400 µg/d	55	Additional 32% decrease in OCS dose by ≥50%
Kass et al, ¹⁸ 1977	29 adults	Beclomethasone dipropionate, 400–1,000 µg/d	86	
Lee-Hong and Collins-Williams, ¹⁹ 1977	17 adults and children*	Beclomethasone dipropionate, 400 µg/d	71	
Smith and Hodson, ²⁰ 1983	162 adults	Beclomethasone dipropionate, 500–2,000 µg/d	27	Additional 39% decrease in OCS dose
Triamcinolone				
Williams, ²¹ 1975	35 adults	Triamcinolone acetonide, 800–2,000 µg/d	40	Additional 43% discontinued OCS use but required occasional short courses
Sly et al, ²² 1978	5 children	Triamcinolone acetonide, 200–1,200 µg/d	60	
Golub, ²³ 1980	26 adults	Triamcinolone acetonide, 800 µg/d	60	
Flunisolide				
Slavin et al, ²⁴ 1980	73 adolescents and adults	Flunisolide, 1,000 µg/d	27	Additional 47.5% decrease in OCS dose by ≥50%
Shapiro et al, ²⁵ 1981	32 children and adolescents	Flunisolide, 1,000 µg/d	6	
Orgel et al, ²⁶ 1983	34 children	Flunisolide, 1,000 µg/d	...	
Fluticasone propionate				
Noonan et al, ²⁷ 1995	96 adults and adolescents	Fluticasone propionate, 1,500 µg/d	69	Mean OCS dose decrease of 6.6 mg/d
		Fluticasone propionate, 2,000 µg/d	88	Mean OCS dose decrease of 9.3 mg/d
Nimmagadda et al, ²⁸ 1998	13 adults	Fluticasone propionate, 1,000 µg/d	...	Decrease in OCS dose but required intermittent short courses
		Fluticasone propionate, 2,000 µg/d	100	
Nelson et al, ²⁹ 1999	111 adults and adolescents	Fluticasone propionate, 1,000 µg/d	75	Additional 10% decrease in OCS dose by ≥50%
		Fluticasone propionate, 2,000 µg/d	89	Additional 8% decrease in OCS dose by ≥50%
Westbroek et al, ³⁰ 1999	301 adults and adolescents	Fluticasone propionate nebulas, 1 mg/d	26	Median OCS dose decrease of 50%
		Fluticasone propionate nebulas, 4 mg/d	37	Median OCS dose decrease of 67%
McMurtry and Nimmagadda, ³¹ 2001	5 children and adolescents	Fluticasone propionate, 2,000 µg/d†	20	OCS dose decreased by 66% over 12 months
Budesonide				
Ädelroth et al, ³² 1985	38 adults	Budesonide, 200–1,600 µg/d	47	Additional 29% decrease in OCS dose by ≥50%
Crowe et al, ³³ 1986	29 children and adults	Budesonide, 1,600 µg/d	28	Additional 31% decrease in OCS dose by ≥50%
Laursen et al, ³⁴ 1986	50 adults	Budesonide, 400 µg/d	40	OCS dose decreased by 39% after 15 weeks
		Budesonide, 1,600 µg/d		OCS dose decreased by 54% after 15 weeks; 96% of remaining patients (n = 45) decreased OCS dose throughout 51 weeks

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Table 1. Continued from page 514

Study	Study population	Treatment	Patients discontinuing OCS use, %	Additional outcomes
De Jongste and Duiverman, ³⁵ 1989	56 infants and children	Budesonide inhalation suspension, 0.5–2.5 mg/d	100‡	OCS short courses decreased from 2.2 per child per year to 0.9 per year of follow-up
Otulana et al, ³⁶ 1992	18 adults	Budesonide inhalation suspension, 4–8 mg/d	78	Additional 17% decrease in OCS dose by ≥50%
Ilangoan et al, ³⁷ 1993	36 children	Budesonide inhalation suspension, 2 mg/d	...	OCS dose decreased by 80%
de Blic et al, ³⁸ 1996	40 infants	Budesonide inhalation suspension, 2 mg/d	NA	Lower median duration of OCS therapy with budesonide vs placebo
Nelson et al, ³⁹ 1998	159 adults	Budesonide, 800 µg/d	68	OCS dose decreased by 83%
Childhood Asthma Management Program, ⁴⁰ 2000	1,041 children	Budesonide, 1,600 µg/d	64	OCS dose decreased by 79%
		Budesonide, 400 µg/d	NA	43% lower rate of OCS short courses with budesonide vs placebo
Miyamoto et al, ⁴¹ 2000	113 adults	Budesonide, 800 µg/d	15	Additional 33% decrease in OCS dose by ≥50%
Leflein et al, ⁴² 2002	335 children	Budesonide, 1,600 µg/d	23	Additional 45% decrease in OCS dose by ≥50%
		Budesonide inhalation suspension, 0.5 mg/d	NA	47% required OCS short courses compared with 70% receiving cromolyn

Abbreviations: NA, not applicable; OCS, oral corticosteroid.

* Study included patients aged 6 to 20 years. Only 17 of the original 20 patients were still receiving beclomethasone dipropionate at the end of the 34-month follow-up study.

† Mean daily inhaled corticosteroid dose.

‡ All 5 children taking daily prednisone were weaned off oral therapy.

budesonide, 400 µg twice daily; 60% in patients taking budesonide, 800 µg twice daily; and 9% in patients receiving placebo. The proportion of patients who could discontinue OCS use was greater in both budesonide groups compared with the placebo group. In each of these DPI studies, lung function and asthma symptom scores improved in the budesonide groups but declined in the placebo groups.

The efficacy of nebulized budesonide in reducing the need for OCSs also has been demonstrated in adults. In an open-label trial of patients receiving daily prednisolone and high-dose ICSs for asthma control who failed 1 or more attempts at reducing their OCS use, the mean daily prednisolone dose was significantly reduced from 17.6 mg at baseline to 3.2 mg after 1 year of nebulized budesonide treatment (2 to 4 mg twice daily).³⁶ Fourteen patients also successfully discontinued OCS use. Patients experienced moderate improvements in lung function when switched from conventional ICS therapy to nebulized ICS therapy, and the mean annual number of acute asthma exacerbations requiring hospitalization declined from 1.5 to 0.9.

The ability of nebulized budesonide to reduce OCS requirements in children younger than 5 years with severe asthma was evaluated in a double-blind, placebo-controlled study. Treatment with nebulized budesonide (1.0 mg twice daily) for 8 weeks enabled prednisolone dose reductions of 80% compared with 41% for children given placebo.³⁷

Among children younger than 2 years, oral prednisolone use was discontinued in 5 of 8 children treated with budesonide compared with 1 of 8 given placebo. Children switched from placebo to budesonide during an 8-week, open-label follow-up period were subsequently able to further reduce their oral prednisolone doses.

In a randomized, double-blind study of young children (<30 months) with severe asthma, those who received budesonide inhalation suspension, 1 mg twice daily for 12 weeks, had a significantly lower median duration of OCS therapy compared with those who received placebo (0% vs 14.5% of total treatment time).³⁸ An uncontrolled study of infants and preschool children with frequent severe asthma exacerbations despite maintenance asthma treatment further demonstrated that nebulized budesonide (initially 0.5 to 2.5 mg/d) reduced prednisone use from 2.2 courses per patient per year to 0.9 per patient per year of follow-up. All 5 patients who required daily oral prednisone were weaned off prednisone during budesonide treatment.³⁵ Additionally, the effectiveness of nebulized budesonide (0.5 mg daily) in reducing the need for OCSs to control exacerbations was compared with that of nebulized cromolyn sodium (20 mg 4 times daily) in a year-long study of young children (2 to 6 years) with mild or moderate persistent asthma. Only 47% of children treated with budesonide required short courses of OCSs compared with 70% treated with cromolyn sodium. Additionally, children re-

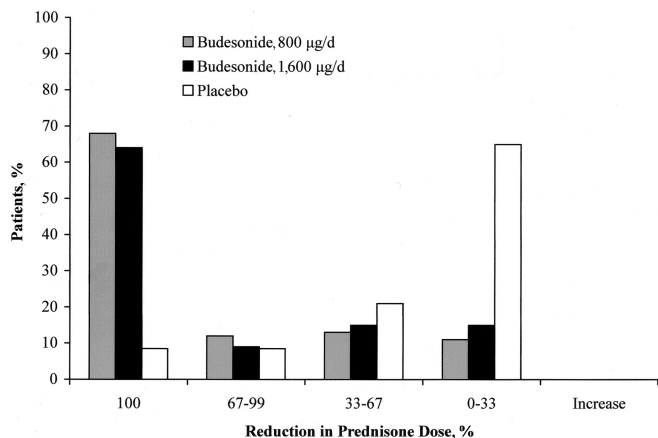


Figure 1. The percentage of patients who showed reductions of 100%, 67% to 99%, 33% to 67%, 0 to 33%, or an increase in their prednisone dose after 20 weeks of treatment with 800 µg/d of budesonide inhalation powder (400 µg twice daily), 1,600 µg/d of budesonide inhalation powder (800 µg twice daily), or placebo. Reprinted from Nelson et al.³⁹

ceiving budesonide used OCSs for significantly fewer days than children given cromolyn sodium (mean, 6.3 vs 9.3 days per year).⁴² A reduced requirement for short courses of OCSs was also demonstrated with budesonide administered via Turbuhaler in a double-blind, placebo-controlled, randomized trial of children with mild-to-moderate persistent asthma.⁴⁰ Children treated for 4 to 6 years with budesonide, 400 µg twice daily, had a 43% lower rate of short courses of oral prednisone for asthma exacerbations compared with children given placebo (Figure 2). Overall, these studies indicate that budesonide administered via pMDI, Turbuhaler, or nebulizer is effective at reducing both long-term OCS requirements and short-course OCS therapy in adult and pediatric patient populations.

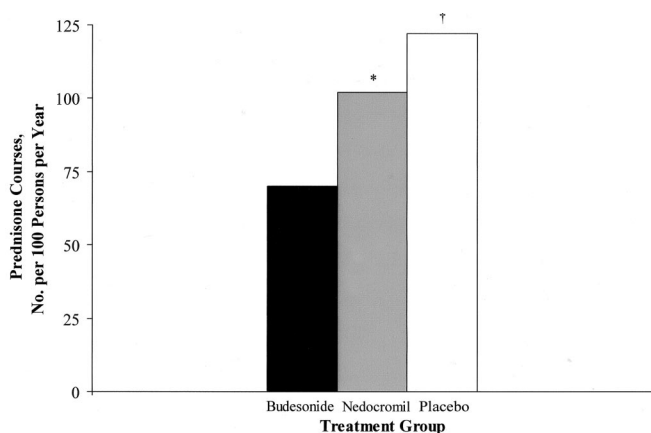


Figure 2. Number of short courses of prednisone required per 100 person-years in 1,041 children treated with budesonide inhalation powder, nedocromil sodium, or placebo for 4 to 6 years. * $P < .001$, † $P < .01$. Data obtained from The Childhood Asthma Management Program Research Group.⁴⁰

Fluticasone Propionate. Introduced in the United States in 1996, fluticasone propionate is a relatively new ICS available as both a pMDI (Flovent Inhalation Aerosol, GlaxoSmithKline, Research Triangle Park, NC) and a DPI (Flovent Rotadisk, GlaxoSmithKline). Fluticasone propionate is also available outside the United States as a nebulized formulation (Flixotide Nebules, GlaxoSmithKline, Boronia, Victoria) for prophylactic management of severe chronic asthma in adults and adolescents older than 16 years and treatment of acute exacerbations in those aged 4 to 16 years. This molecule has a high affinity for glucocorticoid receptors.^{62,63} Clinical trials have shown that inhaled fluticasone improves lung function and symptom scores in patients with asthma.⁶⁴⁻⁶⁶

Several studies have evaluated the OCS-sparing effects of fluticasone DPI in patients with severe persistent asthma. As part of a larger double-blind, multicenter trial, a single-center study evaluated the OCS dose reduction in 13 adults who were initially receiving both ICSs and OCSs.²⁸ Patients switched from other ICSs with OCS therapy to fluticasone DPI, 1,000 µg twice daily, successfully discontinued use of oral prednisone within 16 weeks and maintained this status at 52 weeks. Patients switched to fluticasone, 500 µg twice daily, reduced their OCS dose; however, 2 required intermittent short courses of oral therapy. Lung function improved in both treatment groups. Although those patients switched to placebo reduced their prednisone doses, all had to withdraw from the study because of poor asthma control.

Similar results were obtained in a study of adolescents and adults who required 5 to 40 mg/d of prednisone to control their asthma.²⁹ This study found that 75% and 89% of patients treated with fluticasone via DPI (500 µg twice daily or 1,000 µg twice daily, respectively) discontinued OCS use compared with 9% of patients given placebo (Figure 3). Patients who received the higher dose of fluticasone showed significant

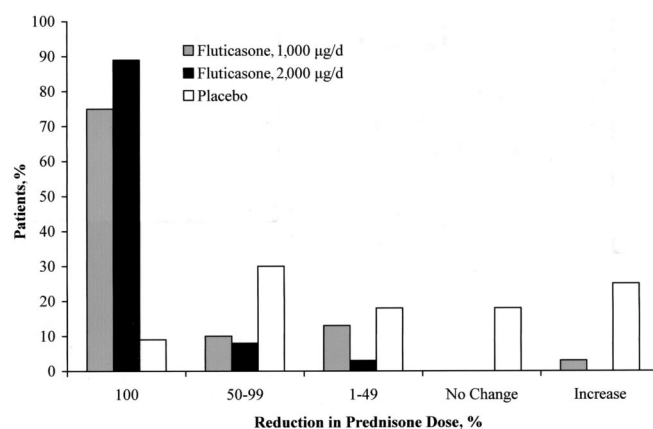


Figure 3. The percentage of patients who showed reductions of 100%, 50% to 99%, or 1% to 49%, no change, or an increase in their prednisone dose after 16 weeks of treatment with 1,000 µg/d of fluticasone propionate inhalation powder (500 µg twice daily), 2,000 µg/d of fluticasone propionate inhalation powder (1,000 µg twice daily), or placebo. Reprinted from Nelson et al.²⁹

improvements in lung function and symptom control compared with patients given placebo. Although these parameters improved in patients given the lower dose, differences compared with placebo were not always significant.

Fluticasone pMDI also has been effective in reducing OCS requirements in severe asthma. In a study of adolescents and adults, oral prednisone use was discontinued by 69% and 88% of those who received fluticasone, 750 μg and 1,000 μg twice daily, respectively.²⁷ The mean daily OCS dose also decreased significantly in each fluticasone group ($n = 32$ for each group) compared with a 1.6-mg/d increase in the placebo group ($n = 32$). Both fluticasone groups showed significant improvements in lung function and asthma symptom scores compared with placebo.

The OCS-sparing effects of nebulized fluticasone for severe asthma also have been evaluated. In a 12-week, randomized, double-blind, placebo-controlled study of patients aged 19 to 83 years, daily oral prednisolone doses were reduced to a significantly greater extent in patients given 2 mg twice daily ($n = 103$) of nebulized fluticasone than in patients given 0.5 mg twice daily ($n = 102$) or placebo ($n = 96$) (adjusted means, 4.44 vs 2.16 and 1.20 mg, respectively).³⁰ Of the 240 patients who completed the study, those who received fluticasone, 2 mg twice daily, were more likely to discontinue prednisolone use compared with those who received the lower dose of fluticasone or placebo. Although reductions in OCS use were accompanied by improvements in lung function, there were no significant differences between groups.

The only report of the OCS-sparing effects of fluticasone in children involved a retrospective medical record review from 5 pediatric patients (aged 8 to 16 years) with asthma who were dependent on both ICSs and OCSs. After switching to inhaled fluticasone (mean dose, 1,480 $\mu\text{g}/\text{d}$), OCS doses decreased by 66% after 12 months, with 1 patient discontinuing oral treatment completely.³¹ Furthermore, forced expiratory volume in 1 second (FEV_1) improved significantly.

These studies indicate that high-dose fluticasone is effective in reducing OCS requirements in adult patients with severe persistent asthma. Additional studies in children are needed to confirm the effectiveness of this ICS in reducing OCS use in pediatric patients with severe persistent asthma.

EFFICACY OF ICSs VS OCSs FOR THE MANAGEMENT OF ACUTE ASTHMA EXACERBATIONS

There is limited evidence that ICSs may be effective for treating acute asthma exacerbations, and administering ICSs in these circumstances could reduce the need for short courses of OCSs. For example, in 403 adult patients experiencing a mild exacerbation that clinicians believed required a short course of OCS treatment, a 16-day course of inhaled fluticasone (1 mg twice daily via MDI) was as effective as a tapering course of oral prednisolone in preventing treatment failures, which were defined as a 60% reduction in personal

best peak expiratory flow rate (PEFR) or persistent symptoms.⁶⁷ Similarly, a study of 321 children (mean age, 9 years) with an acute exacerbation of asthma found that nebulized fluticasone (1 mg twice daily), which is not available in the United States, was at least as effective as oral prednisolone (1 to 2 mg/d) in improving lung function. Mean morning PEFR increased from 178 ± 68 to 255 ± 88 L/min in the fluticasone group compared with 183 ± 70 to 227 ± 84 L/min in the oral prednisone group. Evening PEFR and symptom scores improved similarly in both groups.⁶⁸ Other studies, however, have reported less favorable outcomes. Children 5 years or older ($N = 100$) with severe acute asthma (baseline FEV_1 , approximately 45% predicted) fared significantly worse after treatment with fluticasone (single 2-mg dose via pMDI with spacer) compared with children given oral prednisone (2 mg/kg).¹² One study assessing the effectiveness of adding high-dose flunisolide (1 mg via pMDI with spacer every 10 minutes for 3 hours) to salbutamol in adult patients presenting to the emergency department with severe acute asthma demonstrated significant improvements in FEV_1 and PEFR compared with placebo as early as 90 minutes after treatment initiation.^{69,70} Studies assessing the effectiveness of beclomethasone dipropionate have yielded mixed results, providing limited evidence that beclomethasone may be useful for managing acute asthma exacerbations.^{71,72}

Studies of adults or children treated with inhaled budesonide provide consistent evidence of the effectiveness of this ICS for managing acute asthma exacerbations. One study compared the effectiveness of nebulized budesonide (2 mg twice daily) with that of 30-mg oral prednisolone once daily when each was given with nebulized albuterol (5 mg 4 times daily) in 19 adults with corticosteroid-responsive asthma or chronic obstructive pulmonary disease who were experiencing acute bronchospasm.⁷³ Improvements in FEV_1 were similar in both treatment groups; FEV_1 increased from 1.8 to 2.1 L and 1.9 to 2.0 L for prednisolone and budesonide, respectively. In another study of 84 adults, those randomized to treatment with budesonide, 1,600 μg twice daily, via Turbuhaler for 1 week after an acute exacerbation did as well as those treated with oral prednisolone (tapered from 40 to 5 mg/d).⁷⁴ Improvements in FEV_1 , PEFR, and symptom scores did not differ significantly between treatment groups. Likewise, a randomized trial involving 185 patients found that patients treated with budesonide, 2,400 μg once daily, for 7 to 10 days after emergency department discharge did not differ from those treated with prednisone, 40 mg once daily, with regard to relapse rate or improvements in FEV_1 , PEFR, symptom scores, or asthma quality-of-life scores.⁷⁵

Eighty children (aged 2 to 12 years) with acute moderate-to-severe exacerbations were randomized to receive either (1) oxygen, a single dose of oral prednisolone (2 mg/kg), nebulized albuterol, and placebo nebulization; or (2) oxygen, a single dose of oral placebo, nebulized albuterol, and nebulized budesonide (800 μg).¹³ In both groups, the nebulizer treatments were given at admission and subsequent 30-minute intervals for 3 doses. Improvements in mean respira-

tory rate, heart rate, pulmonary index, and respiratory distress were significantly greater in the budesonide group. In addition, the improvement in respiratory distress occurred significantly faster with budesonide treatment (1.7 hours) compared with prednisolone (2.5 hours). Another randomized, double-blind, placebo-controlled study compared the effects of nebulized budesonide (2 mg every 8 hours) and oral prednisolone (2 mg/kg up to 40 mg at randomization and at 24 hours) in 46 hospitalized children with severe asthma exacerbations.¹⁴ At 24 hours, FEV₁ was significantly increased from baseline in the budesonide group (49.9%) but not the prednisolone group (22.6%). Coughing severity, wheezing severity, pulse rates, and respiratory rates improved similarly and significantly in both treatment groups; however, severity of shortness of breath decreased significantly more with budesonide than with prednisolone. A third study in 22 children (aged 6 to 16 years) treated for moderately severe asthma attacks¹⁶ revealed comparable improvements in PEFr, pulmonary index score, wheezing, accessory muscle use, and oxygen saturation 4 hours after a single dose of budesonide (1,600 μg) administered via Turbuhaler or prednisolone (2 mg/kg). In addition, children treated with budesonide showed a superior clinical response during the first week after discharge compared with children in the prednisolone group.

These studies demonstrate that ICSs may be effective for treating acute asthma exacerbations in children and adults. Similarly, a recent meta-analysis that examined the evidence supporting ICS treatment of acute asthma in the emergency department found a beneficial effect on hospital admission rates and percentage of predicted FEV₁ at 2 hours.⁷⁶ However, this latter benefit was small and of questionable clinical relevance. The studies reviewed herein and in the meta-analysis suggest that there is not enough evidence to support routine use of ICSs in place of systemic corticosteroids for acute asthma.

Budesonide has been studied more frequently than other ICSs for use in this capacity. In a double-blind trial, 188 patients were randomized to receive oral prednisone (50 mg once daily) plus placebo or budesonide (800 μg twice daily via Turbuhaler) following emergency department discharge.⁷⁷ After 21 days, the budesonide group had a 48% lower relapse rate, significantly improved asthma quality-of-life and symptom scores, and significantly less β₂-agonist use compared with placebo.⁷⁷ Thus, administration of an ICS in addition to OCSs during periods of asthma worsening may assist in reducing a patient's total corticosteroid exposure because a lower OCS dose might be required.

SAFETY OF ICSs IN OCS-SPARING STUDIES

Successful reduction of OCS use often requires therapy with high ICS doses that have the potential to produce systemic effects. However, such systemic effects are usually less than those produced with OCSs.⁹ In studies involving first-generation ICSs, patients have often shown at least partial recovery

from deficits in hypothalamic-pituitary-adrenal (HPA) axis function when switched from OCS to ICS therapy (Table 2).^{18,23–25,43–45,52} A meta-analysis of 27 studies similarly concluded that doses of more than 800 μg/d of inhaled beclomethasone or triamcinolone produced comparable levels of HPA axis suppression that were substantially less than the suppression produced by normal therapeutic doses of prednisolone. However, the ICS dose is important to consider because doses of more than 1,500 μg/d, required by some patients, may be adrenal suppressive.⁹ Furthermore, the formulations of beclomethasone and triamcinolone used in these studies involved pMDIs with chlorofluorocarbon propellant. The systemic activity of OCS-sparing doses of the newer formulations have yet to be fully evaluated.

Three of the OCS-sparing studies with fluticasone evaluated changes in HPA axis function.^{27,29,30} In contrast to the studies with first-generation ICSs, only one of these studies reported improved HPA axis function associated with reduced OCS use.²⁷ These improvements were found only at the lower (750 μg twice daily) of 2 fluticasone doses evaluated.²⁷ Furthermore, one of the studies reported decreased morning plasma cortisol concentrations in patients given a high dose (2,000 μg twice daily) of nebulized fluticasone.³⁰ Thus, appreciable reductions in systemic corticosteroid activity may not accompany the reductions in OCS use achieved with high doses of inhaled fluticasone. This may result from the potency, high lipophilicity, and long half-life of fluticasone compared with other ICSs.⁹

Reductions in OCS use achieved with budesonide, 400 and 800 μg twice daily, in adult patients can result in partial recovery from OCS-induced deficits in HPA axis function (Table 2). In one study, the OCS-sparing effects of budesonide were associated with an increase in the percentage of patients with a normal response to adrenocorticotropic hormone infusion after 51 weeks.³⁴ A second study reported significant improvements from baseline in morning and adrenocorticotropic hormone-stimulated plasma cortisol concentrations after 28 weeks of budesonide therapy.⁴¹ Improvements in basal^{33,39} and stimulated³⁹ cortisol concentrations also were observed in 2 other studies following OCS reduction, although improvements missed achieving statistical significance in one of the studies.³³ These findings concur with conclusions reached by Lipworth,⁹ whose meta-analysis suggested that even doses of 800 μg/d or more of inhaled budesonide produce less suppression of morning plasma and serum cortisol levels than normal therapeutic doses of prednisolone.

Doses of ICS that are effective for reducing OCS requirements appear to be well tolerated by patients. In OCS-sparing trials, adverse events associated with long-term administration of low to high doses of ICSs were generally limited to localized oropharyngeal and respiratory events, were rarely severe, and typically dissipated with continued treatment.^{17–27,29,30,32–36,38} Patients also reported adverse events related to OCS withdrawal that were often more problematic than the ICS-related events.^{17,18,23,29,32,34}

Table 2. Hypothalamic-Pituitary-Adrenal Axis Function with Inhaled Corticosteroid Reduction of Oral Corticosteroid Requirements

Study	Study population	Treatment	Outcome
Beclomethasone			
Harvey et al, ⁴⁴ 1976	32 adults	Beclomethasone dipropionate, 400 µg/d	Morning plasma cortisol levels doubled with decreased OCS dose after 12 weeks
Glazer et al, ⁴³ 1977	15 adults	Beclomethasone dipropionate, 400 µg/d	Urinary 17-OCHS levels normalized with decreased OCS dose after 8 weeks
Kass et al, ¹⁸ 1977	29 adults	Beclomethasone dipropionate, 400–1,000 µg/d	Increase in mean plasma cortisol levels with decreased OCS dose within 3 months of initiating treatment
Webb, ⁴⁵ 1977	30 adults	Beclomethasone dipropionate, 400 µg/d	Increase in morning and metyrapone-stimulated plasma cortisol levels after 12 weeks and 6 months
Triamcinolone			
Falliers, ⁵² 1976	22 adults	Triamcinolone acetonide, 400–1,400 µg/d	Morning and cosyntropin-stimulated plasma cortisol normalized with decreased OCS dose after 4 weeks
Golub, ²³ 1980	26 adults	Triamcinolone acetonide, 800 µg/d	Increase in mean plasma cortisol levels with decreased OCS dose after 12 weeks
Flunisolide			
Slavin et al, ²⁴ 1980	78 adults and adolescents	Flunisolide, 1,000 µg/d	Increase in mean plasma cortisol levels with decreased OCS dose after 16 weeks
Shapiro et al, ²⁵ 1981	32 children and adolescents	Flunisolide, 1,000 µg/d	Similar number of patients with normal morning or cosyntropin-stimulated plasma cortisol levels after 12 weeks
Fluticasone propionate			
Noonan et al, ²⁷ 1995	96 adults and adolescents	Fluticasone propionate, 1,500–2,000 µg/d	Decrease in number of patients with abnormal morning plasma cortisol levels after 16 weeks with lower dose
Nelson et al, ²⁹ 1999	111 adults and adolescents	Fluticasone propionate, 1,000–2,000 µg/d	Trend for increase in peak cosyntropin-stimulated plasma cortisol levels after 16 weeks with lower dose
Westbroek et al, ³⁰ 1999	360 adults and adolescents	Fluticasone propionate, 1,000–4,000 µg/d	Increase in mean serum cortisol values after 12 weeks with higher dose
Budesonide			
Crowe et al, ³³ 1986	29 children and adults	Budesonide, 1,600 µg/d	Increase in mean plasma cortisol levels with decreased OCS dose at last visit
Laursen et al, ³⁴ 1986	50 adults	Budesonide, 400 µg/d	Increase in percentage of patients with normal response to ACTH with decreased OCS dose after 51 weeks
Nelson et al, ³⁹ 1998	159 adults	Budesonide, 800–1,600 µg/d	Nonsignificant increase in morning and ACTH-stimulated plasma cortisol levels with decreased OCS dose after 20 weeks
Miyamoto et al, ⁴¹ 2000	113 adults	Budesonide, 800–1,600 µg/d	Increase in morning and ACTH-stimulated plasma cortisol levels with decreased OCS dose after 28 weeks

Abbreviations: ACTH, adrenocorticotropic hormone; 17-OCHS, 17-hydroxycorticosteroid; OCS, oral corticosteroid.

CONCLUSION

Studies in both children and adults indicate that ICSs can enable patients with persistent asthma to reduce, and often eliminate, OCS requirements. The stabilization of asthma with ICS therapy and the ability of ICSs to control asthma attacks also reduce the need for short courses of OCSs to manage exacerbations. Although first-generation ICSs revolutionized asthma management, recent data suggest that of the currently available ICSs, budesonide and fluticasone appear to be the most efficacious at improving lung function

and controlling asthma symptoms when used as OCS-sparing agents. Of these 2 agents, budesonide is the most intensively studied. Data on the OCS-sparing effects of fluticasone in children are limited, and its use in acute asthma is not consistently supported.

Despite the potential for relatively high levels of systemic corticosteroid activity with high doses of fluticasone, ICSs are generally well tolerated when used to decrease OCS requirements for the long-term control of severe asthma or as step-up therapy for acute exacerbations. Overall, OCS-spar-

ing effects of ICSs improve the safety of asthma therapy by minimizing the extent of systemic corticosteroid exposure. Reductions in OCS use achieved with budesonide therapy, for example, are consistently associated with at least partial recovery of HPA axis function. Thus, evidence supports the use of ICSs, in particular, budesonide, to reduce OCS treatment requirements and improve the overall safety of asthma therapy in children and adults with severe persistent asthma.

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